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(54) Title: A METHOD FOR TREATING HERPES VIRUSES

(57) Abstract: The present invention relates to a method for selecting an anti-herpes viral compound and a method for selectively inhibiting herpesvirus in a human host in need of such treatment. The present invention relates to a method for selecting an anti-herpes viral compound and a method for selectively inhibiting herpesvirus in a human host in need of such treatment.

A METHOD FOR TREATING HERPES VIRUSES

FIELD OF THE INVENTION

The present invention relates to a method for selecting an anti-herpes viral
5 compound and a method for selectively inhibiting herpes viruses in a human host in need of such treatment.

BACKGROUND OF THE INVENTION

The herpesviruses comprise a large family of double stranded DNA viruses. Eight
10 of the herpes viruses, herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), varicella zoster virus (VZV), human cytomegalovirus (HCMV), Epstein-Barr virus (EBV), and human herpes viruses 6, 7, and 8 (HHV-6, HHV-7, and HHV-8), have been shown to infect humans. Several of these viruses are important human pathogens.

HSV-1 is estimated to affect 100 million people in the U.S. Primary infection of
15 HSV-1 usually occurs between the ages of one and four. Cold sores, the visible symptom, typically appear at a later age, with 20-45% of the population over the age of fifteen affected (Whitley, Clin. Infect. Dis., 26:541-555, 1998).

Genital herpes (HSV-2) is the second most common sexually transmitted disease, with approximately 22% of the U.S population infected with this virus (Fleming 1997).

20 VZV is the causative agent of chicken pox upon primary infection and can recur in adults as zoster.

EBV results in approximately two million cases of infectious mononucleosis in the U.S. each year. It can also cause lymphomas in immunocompromised patients and has been associated with Burkitt's lymphoma, nasopharyngeal carcinoma, and Hodgkins disease.

25 Infection with HCMV often occurs during childhood and is typically asymptomatic except in immunocompromised patients where it causes significant morbidity and mortality.

HHV-6 is the causative agent of roseola and may be associated with multiple sclerosis and chronic fatigue syndrome. HHV-7 disease association is unclear, but it may
30 be involved in some cases of roseola. HHV-8 has been associated with Kaposi's sarcoma, body cavity based lymphomas, and multiple myeloma.

These viruses are capable of residing in a latent state within the host. Reactivation of latent virus results from response to environmental stimuli (ex. UV exposure, stress,

etc.). Infections or recurrence can be life threatening in immunocompromised patients such as AIDS or transplant patients where HCMV can result in retinitis, pneumonia, and gastrointestinal disease.

The increased immunocompromised population has created an unmet medical need
5 for antivirals against herpesviruses because current therapies do not have a sufficiently broad spectrum against this family of viruses and/or they have limited utility due to toxicity. The present invention provides a method for selectively inhibiting herpesviruses DNA polymerase with compounds that have broad spectrum activity. The method offers a distinct advantage in the treatment of patients in need, particularly immunocompromised
10 patients at risk of infection or reactivation by many members of the herpesvirus family.

SUMMARY OF THE INVENTION

The present invention provides a method of selecting compounds that inhibit herpes viruses comprising:

- 15 a) measuring IC_{50} of a compound of interest that inhibits a wild type herpes virus,
- b) measuring IC_{50} of the same compound that inhibits a binding domain mutant herpes virus which is the same strain of the wild type herpes virus,
- c) comparing IC_{50} of step a with IC_{50} of step b; and
- d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times
20 greater than the IC_{50} of step a.

In above method, the order of step a and step b are interchangeable.

The present invention further provides a method of selecting compounds that inhibit herpes viruses comprising:

- a) measuring IC_{50} of a compound of interest that inhibits a wild type HSV-1,
- 25 b) measuring IC_{50} of the same compound that inhibits a binding domain mutant HSV-1 which is the same strain of the wild type herpes virus,
- c) comparing IC_{50} of step a with IC_{50} of step b; and
- d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times
greater than the IC_{50} of step a.

30 In above method, the order of step a and step b are interchangeable.

The present invention further provides a method of selecting compounds that inhibit herpes viruses comprising:

- a) measuring IC_{50} of a compound of interest that inhibits a wild type HSV-2,

- b) measuring IC_{50} of the same compound that inhibits a binding domain mutant HSV-2 which is the same strain of the wild type herpes virus,
- c) comparing IC_{50} of step a with IC_{50} of step b; and
- d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times greater than the IC_{50} of step a.

In above method, the order of step a and step b are interchangeable.

The present invention further provides a method of selecting compounds that inhibit herpes viruses comprising:

- a) measuring IC_{50} of a compound of interest that inhibits a wild type HCMV,
- b) measuring IC_{50} of the same compound that inhibits a binding domain mutant HCMV which is the same strain of the wild type herpes virus,
- c) comparing IC_{50} of step a with IC_{50} of step b; and
- d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times greater than the IC_{50} of step a.

In above method, the order of step a and step b are interchangeable.

The present invention further provides a method for selectively treating diseases caused by herpes viruses in a human host comprising administering a compound to a human in need of such treatment wherein said compound inhibits herpes viruses by interaction with the binding domain in the viral DNA polymerase.

The present invention further provides method for selectively inhibiting herpes viruses in a human host comprising administering a compound to a human in need of such treatment wherein IC_{50} of the compound that inhibits a binding domain mutant herpes virus is at least 3 times greater than IC_{50} of the compound that inhibits a wild type herpes virus which is the same strain as the mutant herpes virus.

The present invention further provides a compound for treating herpesviral infections in a human host wherein IC_{50} of the compound that inhibits a binding domain mutant herpes virus is at least 5 times greater than IC_{50} of the compound that inhibits a wild type herpes virus which is the same strain as the mutant herpes virus.

The present invention further provides a compound for treating herpesviral infections in a human host wherein said compound inhibits the herpesvirus by interacting with the binding domain in the viral DNA polymerase.

The present invention further provides a compound for the inhibiting of herpesvirus DNA polymerases wherein serial passage of a wild type herpes virus in the presence of said

compound results in a change of the wild type HSV-1 polymerase at amino acid 823 from valine to alanine.

The present invention further provides a compound for inhibiting herpesvirus DNA polymerases wherein serial passage of a wild type herpes virus in the presence of said
5 compound results a change of the wild type HCMV polymerase at amino acid 823 from valine to alanine and at amino acid 824 from valine to leucine.

The present invention further provides a mutant herpesvirus DNA molecule having a nucleotide sequence selected from a group consisting of SEQ.ID.NO. 1; SEQ.ID.NO. 3; SEQ.ID.NO. 5; SEQ.ID.NO. 7; SEQ.ID.NO. 9; and SEQ.ID.NO. 11.

10 The present invention further provides a mutant herpesvirus polymerase amino acid molecule having an amino acid sequence selected from a group consisting of SEQ.ID.NO. 2; SEQ.ID.NO. 4; SEQ.ID.NO. 6; SEQ.ID.NO. 8; SEQ.ID.NO. 10 and SEQ.ID.NO. 12.

BRIEF DESCRIPTION OF THE DRAWINGS

15 Figure 1 – examples of 4-oxo-DHQ and 4-oxo-DHTP compounds.

Figure 2 – Herpesvirus' polymerases amino acid conserved region.

Figure 3 – Recovered virus after serial passage of HSV-1 in presence of 20 μ M of compound No. 17.

Figure 4 – Comparision of Wild HSV-1 and HSV-2 herpesvirus DNA polymerase
20 amino acid sequences aligned by amino acid homology. (Seq. No: 14-19)

Figure 5 – Mutant Herpes Virus DNA and amino acid sequence list. (Seq. No: 1-12)

Figure 6 – Wild HCMV herpesvirus DNA polymerases amino acid sequence. (Seq. No 13)

25

DETAILED DESCRIPTION OF THE INVENTION

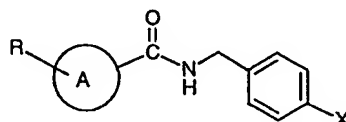
A key enzyme in the replication of all herpesviruses is the virus-coded DNA polymerase. Most of the currently available anti-herpes drugs target the viral DNA polymerase. Drugs such as Foscarnet acts by direct inhibition of the viral polymerase. These drugs are non-nucleoside inhibitors of herpesvirus DNA polymerases. Others such as the
30 nucleoside analogs, Acyclovir, Penciclovir and Ganciclovir must first be phosphorylated to the monophosphate forms by virus encoded kinases and, further phosphorylated to triphosphate by cellular enzymes before they are active inhibitors. The triphosphate forms of these nucleoside analogs inhibit polymerases by competing with the binding of natural

triphosphates and their subsequent insertion into growing DNA strands. These drugs are known as nucleoside inhibitors of herpesvirus DNA polymerases.

One of the limitations of the currently available drugs is that they are active against only a few of the eight human herpesviruses. For example, Acyclovir and Penciclovir inhibit HSV and VZV replication but have poor activity against CMV.

In order to identify antiviral compounds that would have the potential to inhibit replication of most of the human herpesviruses, compounds are *in vitro* screened for inhibitors of herpesvirus DNA polymerase activity. Because portions of the amino acid sequence of the polymerases are highly conserved within the herpesvirus family it is possible to discover small molecules that inhibit herpesvirus polymerases but not cellular DNA polymerases. Using this biochemical approach, several new classes of compounds such as the 4-hydroxyquinoline derivatives (4-HQ), 4-oxo-dihydroquinoline derivatives (4-oxo-DHQ) and 4-oxo-dihydrothienopyridine derivatives (4-oxo-DHTP) were discovered as potent, non-nucleoside herpesvirus DNA polymerase inhibitors. *In vitro* polymerase assays and/or *in vivo* cell culture assays have demonstrated that these compounds inhibit HSV-1, HSV-2, HCMV, VZV, EBV, and HHV-8 replication.

4-Oxo-DHQ and 4-oxo-DHTP are derivatives of formula I



I

wherein ring A is a saturated or unsaturated fused double or triple heterocyclic ring having 1, 2, 3 or 4 heteroatoms selected from group consisting of oxygen, sulfur, or nitrogen; and wherein R and X are the appropriated substituents, respectively.

Examples of 4-HQ compounds, 4-oxo-DHQ compounds and 4-oxo-DHTP compounds are illustrated in **Figure 1**.

Antiviral activity of these examples are shown in Table 1 below. As shown in Table 1, these compounds inhibit HSV-1 and HSV-2 as well or better than the current commercially available drug Acyclovir.

Table 1
Antiviral Activity of 4-oxo DHQ/4-oxo DTHP Against HSV-1 and HSV-2

virus	Compound IC ₅₀ (uM)					ACV
	1	2	3	4	5	
HSV-1 KOS	2.0	3.8	3.2	3.2	3.3	3.6
HSV-1 F	2.5	2.3	2.2	2.1	2.6	1.3
HSV-1 DJL	2.5	2.6	1.8	2.2	2.7	1.8
HSV-1 Patton	ND	5.3	7.7	4.3	10	9.3
HSV-2 MS	2.0	2.5	2.8	2.5	2.5	10
HSV-2 35D	ND	5.4	5.0	3.2	8.1	6.0
HSV-2 186	2.0	2.3	3.2	2.3	4.2	>10

5 It has also been discovered that point mutations within the HSV-1 polymerase gene that confer resistance to Acyclovir and other nucleoside analogs do not result in resistance to the 4-HQ, 4-oxo-DHQs or 4-oxo-DHTPs. Serial passage of wild type HSV-1 in the presence of 4-oxo-DHQ results in the isolation of mutants that are highly resistant (>20 fold increase in the IC₅₀) to these compounds while retaining sensitivity to nucleoside inhibitors
 10 such as Acyclovir.

In order to determine the mechanism of action of 4-HQ, 4-oxo-DHQ and 4-oxo-DHTP compounds against herpes viruses, mutants resistant to these compounds are isolated by serial passage of the virus in the presence of a 4-oxo-DHQ compound. Sequencing analysis of HSV-1 and HSV-2 strains resistant to the 4-oxo-DHQ identifies that HSV-1
 15 (KOS strain) polymerase protein and its homologous HSV-2 have a conserved region (a binding domain), which is a critical contact point for these compounds. While amino acid numbering of the DNA polymerase may vary between strains of HSV-1 and HSV-2, this binding domain encompassing the HSV-1 (KOS) strain amino acid 823 is highly conserved in herpesviruses and can be identified by aligning the homologous amino acids of this
 20 domain as shown in Fig 2.

In HSV-1 and HSV-2 strains resistant to the 4-oxo-DHQ and similar compounds, a change of valine to an alanine at the binding domain provides full resistance.

In the HSV-1 DNA polymerase, resistance is also found when a valine changes to methionine at amino acid 823 but only when accompanied by a second amino acid change.

25 Isolation of HCMV resistant to 4-oxo-DHQ's is found to be very difficult. Comparison of the amino acid sequence of the HSV polymerase (Y-G-F-T-G-V-Q-H-G) and HCMV polymerase (Y-G-F-T-G-V-V-N-G) in the region of amino acid 823 (underlined amino acid) shows that there is a second valine at position 824 in the HCMV

polymerase. In vitro assay using mutant HCMV polymerases demonstrates that full resistance to the 4-oxo-DHQs requires changes at both amino acids 823 (a valine to alanine) and 824 (a valine to leucine). A HCMV polymerase gene containing V823A and V824L mutations is used in marker rescue experiments to generate a viral mutant. This mutant has an IC₅₀ approximately 7-fold above that of wild-type HCMV.

The HSV-1, HSV-2 and HCMV mutants are also found to be resistant to other non-nucleoside inhibitors such as the 4-oxo-DHTP and similar compounds. However, when the binding domain mutants (e. g. HSV-1 V823A, HSV-2-MS V826A, HSV-2-186 V828A, and HCMV V823A/V824L mutants) are tested in plaque reduction assays against a series of nucleoside polymerase inhibitors and the non-nucleoside inhibitor such as Foscarnet, replication of the mutants is found to be inhibited by all of the currently marketed anti-herpes polymerase inhibitors tested.

These studies demonstrate that certain non-nucleosides like 4-HQ, 4-oxo-DHQ and 4-oxo-DHTP compounds bind to a different site on the herpes polymerase than the nucleoside inhibitors and Foscarnet. The valine at the binding domain is conserved in the DNA polymerases of six of the eight human herpesviruses and several animal herpesviruses, and appears to play a critical role in the antiviral activity of the 4-HQ, 4-oxo-DHQ and 4-oxo-DHTP compounds. (See Figure 2)

Since mutation at the binding domain negates these non-nucleoside inhibitors' activities, compounds could be tested against wild type polymerases and the mutant polymerases to establish the probability of similar binding. We refer to this property of compounds as interaction with the binding domain. Since compounds that interact with the binding domain have exhibited broad-spectrum activity against herpesviruses, this invention provides a method for selecting compounds to treat individuals such as immunocompromised patients who are afflicted with multiple herpesvirus infections.

Definitions

The term " wild-type" refers to a gene or gene product which has the characteristics of that gene or gene product when isolated from a naturally occurring source. A wild-type gene is that which is most frequently observed in a population and is thus arbitrarily designated the "normal" or " wild-type" form of the gene.

In contrast, the term "mutant" refers to a gene or gene product which displays modifications in sequence and or functional properties (i.e., altered characteristics) when

compared to the wild-type gene or gene product. It is noted that naturally-occurring mutants can be isolated; these are identified by the fact that they have altered characteristics when compared to the wild-type gene or gene product.

IC₅₀ refers to concentration of a drug that inhibits virus growth by 50%.

5 Wild type HSV-1 and HSV-2 strains are listed in **Figure 4**.

Wild type HCMV is listed in SEQ. ID. NO.13.

The term "Iudr" refers to antiviral drug Iododeoxyuridine.

The term "Bvdu" refers to antiviral drug Bromovinyldeoxyuridine.

The term "ACV" refers to antiviral drug Acyclovir.

10 The term "AraC" refers to antiviral drug Arabinosylcytidine.

The term "AraT" refers to antiviral drug Arabinosylthymine.

The term "AraA" refers to antiviral drug Arabinosyladenine.

The term "GCV" refers to antiviral drug Ganciclovir.

The term "CDV" refers to antiviral drug Cidofovir.

15 The term "PFA" refers to antiviral drug Foscarnet.

The term "binding domain" refers to a conserved region in herpesvirus DNA polymerases. The herpesvirus DNA polymerases have seven (7) conserved regions. The binding domain is within the third conserved region (see Figure 2). When the binding domain contacts with an inhibitor, at least one amino acid in the binding domain mutates and provides the resistance. In general, the binding domain is at an amino acid sequence position 818-829 of the HSV-1 DNA polymerase or the homologous region in other herpes virus DNA polymerases (see Figure 2).

25 The term "a binding domain mutant herpes virus" refers to a herpes virus containing a binding domain mutation.

More specifically, the binding domain in HSV-1 strains, KOS, F, DJL and Patton are at amino acid sequence position 823. The binding domain in HSV-2 MS-M1 strain is at amino acid sequence position 826. The binding domain in HSV-2 186 strain is at amino acid sequence position 828. The binding domain in HCMV AD 169 strains is at amino acid sequence position 823-824.

30 The term "XxxxY" refers to an amino acid sequence position xxx, a single amino acid X in wild type is changed to an amino acid Y.

For example, the term "V823A" refers to an amino acid sequence position 823, a Valine found in wild type is changed to alanine in mutant strain.

The term "V824L" refers to an amino acid sequence position 824, a Valine found in wild type is changed to Leucine in mutant strain.

The term "V826A" refers to an amino acid sequence position 826, a Valine found in wild type is change to alanine in mutant strain.

- 5 The term "V828A" refers to an amino acid sequence position 828, a Valine found in wild type is change to alanine in mutant strain.

A table of amino acids and their representative abbreviations, symbols and codons is set forth below in the following Table.

10

Amino acid	Abbrev.	Symbol	Codon(s)					
Alanine	Ala	A	GCA	GCC	GCG	GCU		
Cysteine	Cys	C	UGC	UGU				
Aspartic acid	Asp	D	GAC	GAU				
Glutamic acid	Glu	E	GAA	GAG				
Phenylalanine	Phe	F	UUC	UUU				
Glycine	Gly	G	GGA	GGC	GGG	GGU		
Histidine	His	H	CAC	CAU				
Isoleucine	Ile	I	AUA	AUC	AUU			
Lysine	Lys	K	AAA	AAG				
Leucine	Leu	L	UUA	UUG	CUA	CUC	CUG	CUU
Methionine	Met	M	AUG					
Asparagine	Asn	N	AAC	AAU				
Proline	Pro	P	CCA	CCC	CCG	CCU		
Glutamine	Gln	Q	CAA	CAG				
Arginine	Arg	R	AGA	AGG	CGA	CGC	CGG	CGU
Serine	Ser	S	AGC	AGU	UCA	UCC	UCG	UCU
Threonine	Thr	T	ACA	ACC	ACG	ACU		
Valine	Val	V	GUA	GUC	GUG	GUU		
Tryptophan	Trp	W	UGG					
Tyrosine	Tyr	Y	UAC	UAU				

MATERIALS AND METHODS

Cell and Viruses

- African green monkey kidney cells (Vero) and human foreskin fibroblast cells (HFF) and herpes viruses can be obtained from the American Type Culture Collection (ATCC). Media is defined as Dulbecco's modified Eagle media (DMEM) containing 10% fetal bovine serum (FBS) and supplemented with antibiotics. Cells are maintained in media at 37°C in a humidified atmosphere of 5% CO₂. HSV-1 strains F, Patton and DJL, HSV-2 strains MS, 35D and 186, and HCMV strain AD169 are used in these studies. Strain DJL is a clinical isolate of HSV-1 isolated in our lab from a primary oral lesion.
- 15
- 20

Measuring IC₅₀ of a Compound of Interest That Inhibits Herpes Viruses

Preparation of Virus Stocks: HSV-1 and HSV-2 stocks are grown in Vero cells. HCMV stocks are grown in HFF cells. Approximately 1 ml of media containing sufficient virus to infect approximately 0.1% to 1% of the cells (multiplicity of infection of 0.001 to 5 0.01 PFU/cell) is added to a T-150 cell culture flask containing a confluent monolayer of cells. The cells are incubated at 37°C for approximately 1 hour. Approximately 50 ml of media is then added to the flask and the cells are incubated at 37°C until viral cytopathic effect (cpe) is apparent in 100% of the cells. The flask is then placed at -80°C for at least 30 min. The flask containing frozen media and cells is placed in a 37°C water bath until the 10 media is thawed. This process disrupts the cells and releases virus into the media. 1 ml aliquots of media containing virus are dispensed into tubes and stored at -80°C. These aliquots of media containing virus are referred to as virus stocks.

Titrating Virus Stocks: Aliquots of virus are thawed at 37°C and serially diluted (10 fold dilutions) in media. 0.1 ml of each dilution of virus is placed in a single well of 24- 15 well cell culture dish containing a confluent monolayer of cells (Vero cells for HSV-1 and HSV-2, HFF cells for HCMV) and incubated at 37°C for 1 h. The virus inoculum is then removed and 1 ml of media containing 0.8% carboxymethylcellulose (CMC) is added to each well of the dish. The dish is incubated at 37°C for approximately 2-3 days (HSV-1 and HSV-2) or 6-9 days (HCMV) to allow sufficient growth of virus to form plaques in the 20 cell monolayer. Plaques can be observed and counted microscopically or by staining the cells with 0.1% crystal violet in 20% ethanol. The virus titer which is expressed as plaque forming units (PFU) per ml is obtained by counting the plaques in a well and correcting for the dilution of the viral inoculum.

Plaque Reduction Assays: Antiviral activity of compounds against herpesviruses such as 25 HSV-1, HSV-2, or HCMV can be measured using plaque reduction assays. 0.1 ml of media containing approximately 50 PFU of virus is added to each well of a 24-well cell culture dish containing a confluent monolayer of cells (Vero cells for HSV-1 and HSV-2, HFF cells for HCMV). Compounds are dissolved in 100% DMSO and diluted in 100% DMSO as 200x stocks of the desired final drug concentration. Typically 5-6 two-fold dilutions are 30 prepared for each compound. Dilutions of compounds are then added to media containing 0.8% CMC resulting in a final 1x drug concentration. After the virus-infected cells have incubated for 1 h at 37°C, the virus inoculum is removed and 1 ml of media containing 0.8% CMC and the various concentrations of compound is added to each well of the dish.

The dish is incubated at 37°C for approximately 2-3 days (HSV-1 and HSV-2) or 6-9 days (HCMV) to allow sufficient growth of virus to form plaques in the cell monolayer. Plaques can be observed and counted microscopically or by staining the cells with 0.1% crystal violet in 20% ethanol. Virus inhibition is determined for each drug concentration by comparing the number of plaques in drug-containing wells to control wells that did not contain drug. Antiviral activity of a compound is expressed as the concentration of compound predicted to reduce the number of plaques in a well by 50% (IC₅₀). The IC₅₀ values are calculated by plotting the per cent inhibition vs. concentration of compound using EXCEL software for linear regression.

Selection of 4-oxo-DHQ resistant HSV-1 and HSV-2

Vero cells are plated out at a density of 3.5×10^5 cells per well in a six well tissue culture plate. Cells are infected with HSV-1 KOS at a multiplicity of infection (moi) of 0.1 pfu/cell and 1 h post infection the cells are overlaid with 3 ml media containing 20 μ M of a 4-oxo-DHQ. Cultures are incubated for 20 h at 37°C, freeze/thawed to release cell-associated virus, and 0.1 ml of culture is used to infect a new monolayer of Vero cells (one passage). Serial passage is repeated seven times in the presence of 20 μ M drug. Virus isolates are then plaque purified three times prior to preparation of stocks. Virus recovered from each passage in the presence of compound No. 17 is shown in Figure 3. 4-oxo-DHQ resistant HSV-1 and HSV-2 may also be selected by the marker transfer method described below using wild-type HSV DNA and the corresponding mutant HSV polymerase gene.

Marker Transfer of a HCMV Mutation

A plasmid containing the wild-type HCMV polymerase gene is modified to contain the V823A or V823A and V824L mutations using a site-directed mutagenesis Kit (Stratagene Corp.) and following the manufactures's protocol. HFF cells are plated into T25 tissue culture flasks to achieve 80% confluency at the time of the transfection. Wild type HCMV AD169 DNA and plasmid DNA containing the mutant HCMV polymerase gene are mixed at a ratio of 1:2 (2ug of viral DNA to 4 ug of plasmid DNA). DNA's are transfected using superfect transfection reagent according to methods recommended by the manufacturer (Quiagen Inc.). Cells are harvested five days posttransfection, freeze-thawed to release virus and half of the sample is used to infect HFF cell monolayers. Cells are overlaid with media containing 20 μ M 4-oxo-DHQ compound 2 (see Figure 1). Serial

passage is repeated seven times in the presence of 20 uM compound 2 and virus isolates are then plaque purified three times prior to preparation of viral stock.

Isolation of HSV and HCMV viral DNA

5 HSV DNA is purified from the cytoplasm of infected Vero cells. Vero cells (50 % confluent) are infected at an multiplicity of 0.01 PFU/cell. At 3-5 days postinfection infected cells (100% cpe) are harvested by centrifugation at 1000 rpm in a Beckman GS-6R centrifuge. The pelleted cells are resuspended in TE buffer and placed on ice for 15 minutes. NP-40 is then added to a final concentration of 0.2% and incubated on ice for a
10 further 15 minutes. The cells are centrifuged at 2000 rpm for 10 minutes in a Beckman GS-6R centrifuge. The supernatant is removed and EDTA is added to a final concentration of 20 mM followed by the addition of SDS to a final concentration of 0.3% and proteinase K to a concentration of 50 ug/ml then incubated at 45C for 2 hours. HCMV DNA is isolated by infecting HFF cells (25% confluency) with HCMV at an multiplicity of 0.1 PFU/cell.
15 Cells and media are harvested 5-7 days postinfection (100% cpe) and subjected to low speed centrifugation to remove intact cells and cell debris followed by a high speed spin to pellet virus particles (2500 rpm's in a Beckman SW28 rotor for 1 hour). Following incubation of the HSV and HCMV samples, 1.5 volumes of saturated NaI is added to the digested extract and the refractive index is adjusted to 1.434 –1.435. Ethidium bromide is
20 added to a final concentration of 50 ug/ml. The samples are loaded into a VTI 50centrifuge tube and spun for 24 hours at 45,000 rpm. The DNA band is harvested extracted three times with n-butanol, then dialyzed against TE buffer followed by a dialysis against 95% ethanol and a final dialysis against TE buffer.

DNA Sequencing

25 HSV-1, HSV-2 or HCMV viral DNA's are sequenced directly using an ABI377 fluorescence sequencer (Perkin Elmer Applied Biosystems, Foster City, CA) and the ABI BigDye PRISMTM dRhodamine Terminator Cycle Sequencing Ready Reaction Kit with AmpliTaq FSTM DNA polymerase (PE Applied Biosystems). Each cycle sequencing
30 reaction contained about 1.0 ug of purified viral DNA. Cycle-sequencing is performed using an initial denaturation at 98°C for 1 min, followed by 50 cycles: 98°C for 30 sec, annealing at 50°C for 30 sec, and extension at 60°C for 4 min. Temperature cycles and times are controlled by a Perkin-Elmer 9700 thermocycler. Extension products are

purified using Centriflex™ gel filtration cartridges (Edge BioSystems, Gaithersburg, MD). Each reaction product is loaded by pipette onto the column, which is then centrifuged in a swinging bucket centrifuge (Sorvall model RT6000B table top centrifuge) at 750 x g for 1.5 min at room temperature. Column-purified samples are dried under vacuum for about 40 min and then dissolved in 4 ul of a DNA loading solution (83% deionized formamide, 8.3 mM EDTA, and 1.6 mg/ml Blue Dextran). The samples are then heated to 90°C for two min, and held at 4°C until loading. 1.5 ul of each sample is loaded into a single well of the ABI377 sequencer. Sequence chromatogram data files from the ABI377 are analyzed with the computer program Sequencer (Gene Codes, Ann Arbor, MI), for assembly of sequence fragments and correction of ambiguous base calls. Generally sequence reads of 600-700 bp are obtained. Potential sequencing errors are minimized by obtaining sequence information from both DNA strands and by re-sequencing difficult areas using primers at different locations until all sequencing ambiguities are removed.

The entire coding region of the polymerase genes from both the parent strains and the resistant viruses are sequenced. The DNA sequencing is done using viral DNA as the template thus avoiding cloning of the polymerase genes. The amino acid sequence of the DNA polymerases of HSV-1 KOS, F, Patton and DJL and HSV-2 MS and 186 are compared in Figure 4. Amino acids that are identical for the six polymerases are shaded in black while regions where amino acid differences are found are shaded in gray. The amino acid sequence of the four HSV-1 polymerases are essentially identical with only a few minor changes noted between the different HSV-1 strains. The majority of amino acid changes are found when the sequences of the HSV-1 and HSV-2 polymerases are compared.

Isolation and Characterization of HSV-1 and HSV-2 Mutants That Are Resistant To the 4-oxo-DHQ's and 4-oxo-DHTP Compounds

A panel of viruses consisting of four strains of HSV-1 (KOS, F, DJL, Patton) and three strains of HSV-2 (MS, 35D, 186) are tested in a plaque reduction assay against four different 4-oxo-DHQ compounds (# 1, 2, 4, 5 as shown in Figure 1), and one 4-oxo-DHTP compound (# 3 as shown in Figure 1) and against Acyclovir. The six drugs inhibited replication of the seven virus strains with IC₅₀ values ranging from 2-10 µM (Table 1). In order to select for 4-oxo-DHQ resistant mutants, HSV-1 strains KOS, F, and DJL along with HSV-2 strains 186 and MS are serially passaged in the presence of 20 uM compound

1. Following the seventh passage, 4-oxo-DHQ resistant virus from each strain are plaque purified three times and high-titer stocks are made. All of the resistant HSV mutants grew to high titers in Vero cells, indicating that the mutations in the resistant isolates did not significantly impair their growth. The mutants selected with 4-oxo-DHQ compound 1 exhibited >10 fold increase in IC₅₀ when tested in a plaque reduction assay against 4-oxo-DHQ compound 1 Data are shown in Table 2.

Table 2

4-oxo-DHQ Resistant Virus of HSV-1 and HSV-2

Virus Mutants	Compound 1 IC ₅₀ (uM)	Amino Acid Change in HSV DNA Polymerase
HSV-1 Kos-M1	>20	- V823A
HSV-1 F-M1	>20	- V823A
HSV-1 DJL-M1	>20	-V823A
HSV-2 MS-M1	>20	- V826A
HSV-2 186-M1	>20	- V828A

- *HSV-1 and HSV-2 isolates grown in the presence of 4-oxo-DHQ select for resistant virus.

DNA sequence analysis of the 4-oxo-DHQ resistant mutants (HSV-1 KOS-M1, HSV-1 F-M1, HSV-1 DJL-M1, HSV-2 186-M1, HSV-2 MS-M1) demonstrated that all five mutants contained a single point mutation of T to C at the binding domain resulting in a Valine to Alanine amino acid change.

Isolation and Characterization of A HCMV Mutant That Is Resistant to The 4-oxo-DHQ's and 4-oxo-DHTP Compounds

- In order to select for a 4-oxo-DHQ HCMV resistant mutant, virus (strain AD169) is serially passaged in the presence of 20 uM a 4-oxo-DHQ. Although we could readily select for HSV mutants using this procedure we failed to isolate an HCMV mutant, even when the virus is passaged at low drug concentrations (<5 uM). Comparison of the amino acid sequence of the HSV polymerase, Y-G-F-T-G-V-Q-H-G, and HCMV polymerase, Y-G-F-T-G-V-V-N-G, in the region of amino acid 823 (underlined amino acid) showed that there is a second valine at position 824 in the HCMV polymerase. In order to determine if both valines need to be changed in order to confer resistance to the 4-oxo-DHQ's, *in vitro* polymerase assays are done using mutant HCMV polymerases containing either V823A or V823A plus V824L (Table 3).

Table 3
HCMV Mutant Polymerase Exhibits Resistance to 4-oxo-DHQ*

Polymerase	Compound 1 IC ₅₀ (uM)
HCMV (wild)	4.6
HCMV V823A	17.2
HCMV V823A/V824L	42.9

*Generation of the valine to alanine at amino acid 823 of HCMV results in a 3.5-fold increase in resistance.

*Mutation of the amino acid from valine to alanine and amino acid 824 from valine to leucine results in an 9-fold increase in resistance, relative to wild type.

The V823A alone resulted in a 3.5-fold increase in the IC₅₀ while the polymerase with the double amino acid change had nearly 10-fold increase in the IC₅₀. In order to isolate an HCMV resistant mutant marker rescue experiments are done. Plasmids containing the mutant polymerase genes are transfected into HFF cells along with wild type HCMV AD169 DNA. The resulting virus is then serially passaged in the presence of 20 uM compound 1 (see figure 1). A 4-oxo-DHQ resistant virus is isolated from marker rescue studies done with the HCMV polymerase gene containing mutations that result in the V823A, V824L amino acid changes, but not with the gene containing V823A change alone. The mutant selected with compound 1 (HCMV AD169-M1) exhibited ~7-fold increase in IC₅₀ when tested in a plaque reduction assay compared to Ganciclovir and

cidofovir which has a \leq 2-fold change in sensitivity (Table 4).

Table 4
Plaque reduction assay of 4-oxo-DHQ resistant HCMV*

Drug	HCMV AD169 IC ₅₀ (μM)	HCMV AD169 – M1 IC ₅₀ (μM)
Compound 1	0.7	4.7
Ganciclovir	0.9	1.0
Cidofovir	0.3	0.6

*Recombination of wild-type HCMV with a polymerase gene containing the valine to alanine at amino acid 823 and the valine to leucine at amino acid 824 allowed for selection of resistant virus with about 7-fold less sensitivity to compound 1.

*Sensitivity of resistant HCMV virus to Ganciclovir and Cidofovir verifies that the 4-oxo-DHQ's mechanism for inhibiting the polymerase protein is unique

The entire coding region of the HCMV polymerase genes from both the parent strain and the resistant virus are sequenced. The DNA sequencing is again done using viral DNA as the template thus avoiding cloning of the polymerase genes. Comparison of the DNA sequence of the two polymerase genes demonstrated that the resistant mutant
5 contained two point mutations that resulted in the predicted V823A, V824L amino acid changes. As with the HSV resistant viruses these results demonstrate the critical role of the region encompassing amino acid 823 for inhibition of polymerase activity by these compounds.

10 **Antiviral Activity of Nucleoside and Non-Nucleoside Polymerase Inhibitors Against 4-oxo-DHQ Resistant Mutants**

In order to determine if the 4-HQ binding domain mutations alter the sensitivity of the HSV-1, HSV-2 and HCMV mutants to both non-nucleoside (4-oxo-DHQ's) and nucleoside inhibitors (e.g Acyclovir and ganciclovir) several of the mutants are tested in
15 plaque reduction assays against a series of non-nucleoside compounds including Foscarnet (PFA), 4-HQ's 4-oxo-DHQ's and 4-oxo-DHTP's (Table 5). The mutants are also tested against a series of nucleoside inhibitors including acyclovir and ganciclovir (Table 5). The activity of these compounds against the mutants is compared to their activity against the wild type strains that are used to isolate the HSV and HCMV mutants. When tested against
20 a number of 4-HQ's, 4-oxo-DHQ's and 4-oxo-DHTP's and other related classes of compounds all of the drugs are found to inhibit the wild type virus with IC₅₀ values ranging from <0.1 uM to 30 uM. When these drugs are tested against the resistant viruses they are found to have IC₅₀ values 5 to 10 fold higher than the parent virus. There is little if any difference in the IC₅₀ values of the nucleoside compounds and the non-nucleoside PFA
25 between the wild type and mutant HSV-1, HSV-2, and HCMV viruses. These results demonstrate that the amino acid change in the binding domain (V823A in the HSV-1 polymerase, V826A in the HSV2-MS polymerase, V828A in the HSV2-186 polymerase, and the V823A/V824L changes in the HCMV polymerase) resulted in resistance to the 4-oxo-DHQ's and 4-oxo-DHTP's, which provides further evidence that these classes of
30 compounds share an affinity for a region we refer to as the binding domain. In contrast, these amino acid changes did not alter the activity of these viruses to other classes of polymerase inhibitors.

Table 5

**Antiviral activity of nucleoside and non-nucleoside polymerase inhibitors
against HSV-1, HSV-2, and HCMV Isolates selected for 4-oxo-DHQ resistance***

Drug	Plaque Reduction Assay – IC ₅₀ (μM)					
	HSV-2 MS	HSV-2 MS-M1	HSV-1 KOS	HSV-1 KOS-M1	HCMV AD169	HCMV AD169-M1
6	28.8	>50	24.6	>50	5.1	>16
7	8.8	27.9	6.5	>50	0.3	3.4
8	2.3	>50	5.1	>50	<0.1	1.1
9	0.9	48.7	1.9	>50	<0.1	3.1
10	29.2	>50	15.8	>50	1.1	>16
11	3.0	>50	3.1	>50	0.7	3.9
12	0.4	12.5	1.3	>50	0.2	1.1
13	5.3	>50	5.5	<25	2.7	>16
14	1.6	>50	28.4	>50	0.9	18.4
2	1.3	>50	3.3	>50	0.4	4.0
4	2.1	28.4	4.2	>50	0.6	2.1
3	0.8	>50	4.0	>50	1.5	6.2
15	5.9	>50	>50	>50	0.7	7.7
Iudr	5.0	6.1	1.1	0.8	ND	ND
Bvdu	5.8	5.9	2.1	0.1	ND	ND
ACV	2.4	2.8	3.9	4.4	ND	ND
AraC	0.2	0.1	0.2	0.2	ND	ND
AraT	6.6	3.6	11.6	3.6	ND	ND
AraA	10.6	18.2	26.1	27.2	ND	ND
GCVir	ND	ND	ND	ND	0.8	0.8
CDV	ND	ND	ND	ND	0.4	0.3
PFA	ND	ND	ND	ND	38	<20

5 *HSV-2 MS, HSV-1 KOS, HCMV AD169: wild type strains

*HSV-2 MS-M1, HSV-1 KOS-M1, HCMV AD169-M1: mutants selected for 4-oxo-DHQ resistance

*ND – Not Done.

Antiviral compounds identified by the present invention can conveniently be
 10 administered in a pharmaceutical composition containing the compound in combination
 with a suitable excipient, the composition being useful in combating viral infections.
 Pharmaceutical compositions containing a compound appropriate for antiviral use are
 prepared by methods and contain excipients which are well known in the art. A generally
 recognized compendium of such methods and ingredients is Remington's Pharmaceutical
 15 Sciences by E.W. Martin (Mark Publ. Co., 15th Ed., 1975).

Antiviral compounds identified by the present invention and their compositions can
 be administered parenterally (for example, by intravenous, intraperitoneal or intramuscular

injection), topically, orally, or rectally, depending on whether the preparation is used to treat internal or external viral infections.

For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

Antiviral compounds identified by the present invention and their compositions can also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

Pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which

are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers. Thickeners such as synthetic polymers, fatty acids,

fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

5 Examples of useful dermatological compositions which can be used to deliver the compounds of formula I to the skin are known to the art; for example, see Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508).

10 Useful dosages of the compounds of formula I can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

The compound is conveniently administered in unit dosage form; for example, containing 5 to 1000 mg, conveniently 10 to 750 mg, most conveniently, 50 to 500 mg of active ingredient per unit dosage form. The desired dose may conveniently be presented in 15 a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.

For internal infections, the compositions can be administered orally or parenterally 20 at dose levels, calculated as the free base, of about 0.1 to 300 mg/kg, preferably 1.0 to 30 mg/kg of mammal body weight, and can be used in man in a unit dosage form, administered one to four times daily in the amount of 1 to 1000 mg per unit dose.

For parenteral administration or for administration as drops, as for eye infections, the compounds are presented in aqueous solution in a concentration of from about 0.1 to 25 about 10%, more preferably about 0.1 to about 7%. The solution may contain other ingredients, such as emulsifiers, antioxidants or buffers.

Generally, the concentration of the compound(s) of formula I in a liquid composition, such as a lotion, will be from about 0.1-25 wt-%, preferably from about 0.5-10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder 30 will be about 0.1-5 wt-%, preferably about 0.5-2.5 wt-%.

The exact regimen for administration of the compounds and compositions disclosed herein will necessarily be dependent upon the needs of the individual subject being treated, the type of treatment and, of course, the judgment of the attending practitioner.

The antiviral activity of a compound of the invention can be determined using pharmacological models which are well known to the art, or using Test A described below.

The compounds of formula (I) and pharmaceutically acceptable salts thereof are useful as antiviral agents. Thus, they are useful to combat viral infections in animals, including man. The compounds are generally active against herpes viruses, and are particularly useful against the varicella zoster virus, the Epstein-Barr virus, the herpes simplex virus, the human herpes virus type 8 (HHV-8) and the cytomegalovirus (CMV).

10

CLAIMS

We claim:

1. A method of selecting compounds that inhibit herpes viruses comprising:
 - a) measuring IC_{50} of a compound of interest that inhibits a wild type herpes virus,
 - 5 b) measuring IC_{50} of the same compound that inhibits a binding domain mutant herpes virus which is the same strain as the wild type herpes virus,
 - c) comparing IC_{50} of step a with IC_{50} of step b; and
 - d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times greater than the IC_{50} of step a.
- 10 2. A method of selecting compounds that inhibit herpes viruses comprising:
 - a) measuring IC_{50} of a compound of interest that inhibits a binding domain mutant herpes virus,
 - b) measuring IC_{50} of the same compound that inhibits a wild type herpes virus which is
 - 15 the same strain as the mutant herpes virus,
 - c) comparing IC_{50} of step a with IC_{50} of step b; and
 - d) selecting the compound of interest wherein the IC_{50} of step a is at least 3 times greater than the IC_{50} of step b.
- 20 3. The method of claim 1 or 2 wherein the herpes virus is HSV-1, HSV-2, HCMV, VZV, EBV, or HHV-8.
4. A method of selecting compounds that inhibit herpes viruses comprising:
 - a) measuring IC_{50} of a compound of interest that inhibits a wild type HSV-1,
 - 25 b) measuring IC_{50} of the same compound that inhibits a binding domain mutant HSV-1 which is the same strain as the wild type herpes virus,
 - c) comparing IC_{50} of step a with IC_{50} of step b; and
 - d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times greater than the IC_{50} of step a.
- 30 5. A method of selecting compounds that inhibit herpes viruses comprising:
 - a) measuring IC_{50} of a compound of interest that inhibits a binding domain mutant HSV-1,

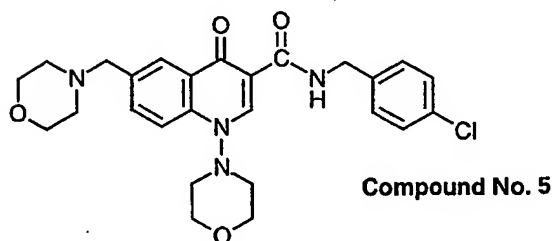
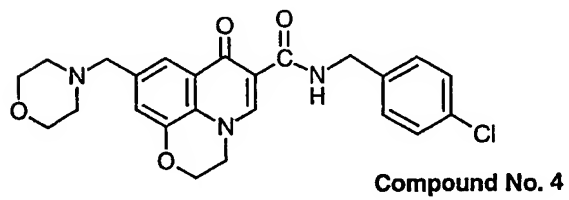
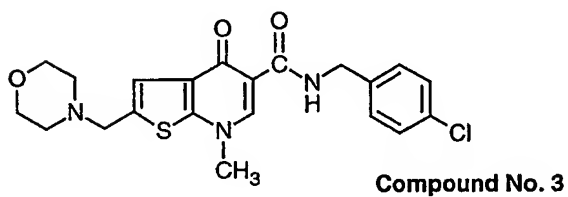
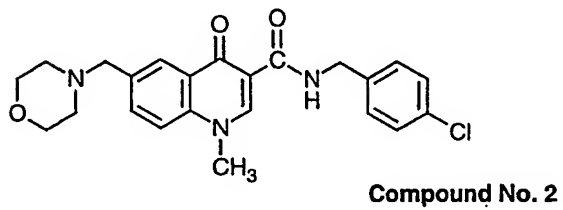
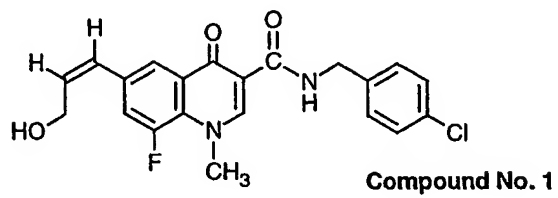
- b) measuring IC_{50} of the same compound that inhibits a wild type herpes virus which is the same strain as the mutant HSV-1,
- c) comparing IC_{50} of step a with IC_{50} of step b; and
- d) selecting the compound of interest wherein the IC_{50} of step a is at least 3 times greater than the IC_{50} of step b.
- 5
6. The method of claim 4 or 5 wherein HSV-1 is HSV-1 KOS, HSV-1 F, HSV-1 DJL or HSV-1 Patton.
- 10 7. The method of claim 5 or 6 wherein the mutation of a wild type herpes virus to mutant herpes virus is at amino acid 823 from valine to alanine.
8. A method of selecting compounds that inhibit herpes viruses comprising:
- a) measuring IC_{50} of a compound of interest that inhibits a wild type HSV-2,
- 15 b) measuring IC_{50} of the same compound that inhibits a binding domain mutant HSV-2 which is the same strain as the wild type herpes virus,
- c) comparing IC_{50} of step a with IC_{50} of step b; and
- d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times greater than the IC_{50} of step a.
- 20
9. A method of selecting compounds that inhibit herpes viruses comprising:
- a) measuring IC_{50} of a compound of interest that inhibits a binding domain mutant HSV-2,
- b) measuring IC_{50} of the same compound that inhibits a wild type herpes virus which is the same strain as the mutant HSV-2,
- 25 c) comparing IC_{50} of step a with IC_{50} of step b; and
- d) selecting the compound of interest wherein the IC_{50} of step a is at least 3 times greater than the IC_{50} of step b.
- 30 10. The method of claim 8 or 9 wherein HSV-2 is HSV-2 MS, HSV-2 35D, or HSV-2 186.
11. A method of selecting compounds that inhibit herpes viruses comprising:

- a) measuring IC_{50} of a compound of interest that inhibits a wild type HCMV,
 - b) measuring IC_{50} of the same compound that inhibits a binding domain mutant HCMV which is the same strain as the wild type herpes virus,
 - c) comparing IC_{50} of step a with IC_{50} of step b; and
 - 5 d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times greater than the IC_{50} of step a.
-
12. A method of selecting compounds that inhibit herpes viruses comprising:
 - a) measuring IC_{50} of a compound of interest that inhibits a binding domain mutant
 - 10 HCMV,
 - b) measuring IC_{50} of the same compound that inhibits a wild type herpes virus which is the same strain of the mutant HCMV,
 - c) comparing IC_{50} of step a with IC_{50} of step b; and
 - d) selecting the compound of interest wherein the IC_{50} of step a is at least 3 times
 - 15 greater than the IC_{50} of step b.
-
13. The method of claim 8 or 9 wherein HCMV is AD169.
-
14. The methods of claims 1, 4, 8, or 11 wherein IC_{50} of step b is at least 5 times greater
 - 20 than the IC_{50} of step a.
-
15. The methods of claims 2, 5, 9, or 12 wherein IC_{50} of step a is at least 5 times greater than the IC_{50} of step b.
-
- 25 16. A use of compounds for manufacturing of medicinals for selectively treating diseases caused by herpes viruses in a human host comprising administering a compound to a human in need of such treatment wherein said compound inhibits herpes viruses by interaction with the binding domain in the viral DNA polymerase.
-
- 30 17. A use of compounds for manufacturing of medicinals for selectively inhibiting herpes viruses in a human host comprising administering a compound to a human in need of such treatment wherein IC_{50} of the compound that inhibits a binding domain

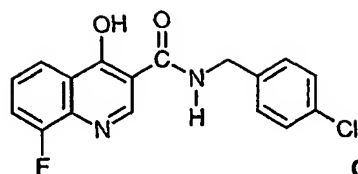
mutant herpes virus is at least 3 times greater than IC_{50} of the compound that inhibits a wild type herpes virus which is the same strain as the mutant herpes virus.

18. The use of claim 17 wherein IC_{50} of the compound that inhibits a binding domain mutant herpes virus is at least 5 times greater than IC_{50} of the compound that inhibits a wild type herpes virus which is the same strain as the mutant herpes virus.
19. The use of claim 17 wherein herpes viruses is HSV-1, HSV-2, HCMV, VZV, EBV, or HHV-8.
20. A use of compounds for manufacturing of medicinals for treating herpesviral infections in a human host wherein IC_{50} of the compound that inhibits a binding domain mutant herpes virus is at least 5 times greater than IC_{50} of the compound that inhibits a wild type herpes virus which is the same strain as the mutant herpes virus.
21. A use of compounds for manufacturing of medicinals for treating herpesviral infections in a human host wherein said compound inhibits the herpesvirus by interacting with the binding domain in the viral DNA polymerase.
22. The herpesviral infection of claim 20 or 21 which is HSV-1, HSV-2, HCMV, VZV, EBV, or HHV-8 infection.
23. A compound for the inhibiting of herpesvirus DNA polymerases wherein passage of a wild type herpes virus in the presence of said compound results a change of the wild type HSV-1 polymerases at amino acid 823 from valine to alanine.
24. A compound for inhibiting herpesvirus DNA polymerases wherein passage of a wild type herpes virus in the presence of said compound results in a change of the wild type HCMV polymerases at amino acid 823 from valine to alanine and at amino acid 824 from valine to leucine.

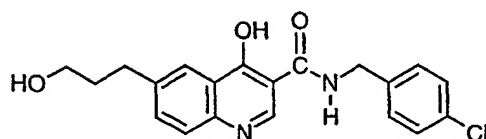
25. A mutant herpesvirus DNA molecule having a nucleotide sequence selected from a group consisting of SEQ.ID.NO. 1; SEQ.ID.NO. 3; SEQ.ID.NO. 5; SEQ.ID.NO. 7; SEQ.ID.NO. 9; and SEQ.ID.NO. 11.
- 5 26. A mutant herpesvirus polymerase amino acid molecule having an amino acid sequence selected from a group consisting of SEQ.ID.NO. 2; SEQ.ID.NO. 4; SEQ.ID.NO. 6; SEQ.ID.NO. 8; SEQ.ID.NO. 10 and SEQ.ID.NO. 12.

Figure 1 **4-HQ, 4-oxo-DHQ and 4-oxo-DHTP antiviral compounds**

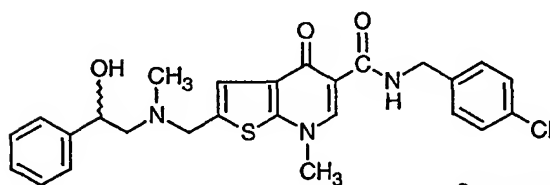
(Figure 1 continue)



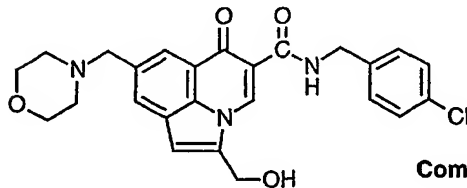
Compound No. 6



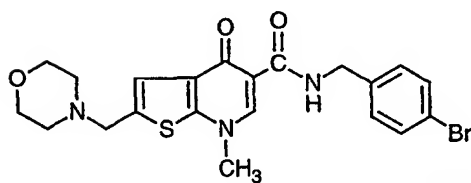
Compound No. 7



Compound No. 8

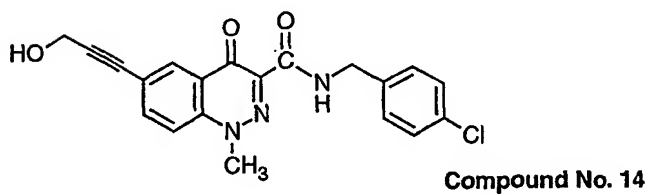
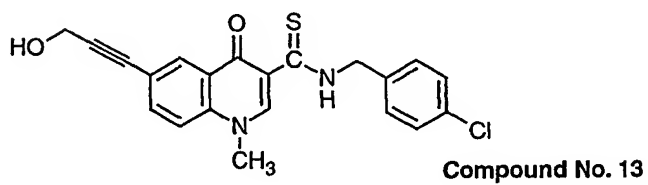
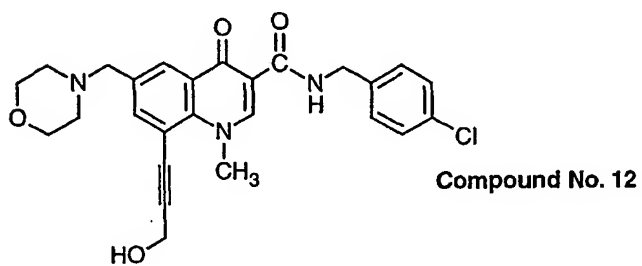
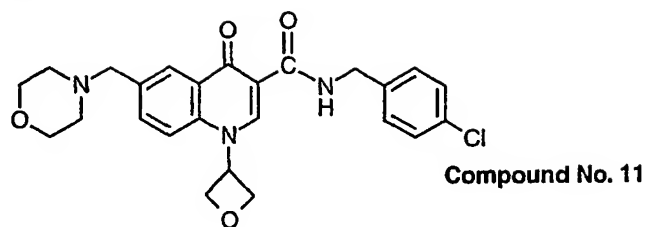


Compound No. 9

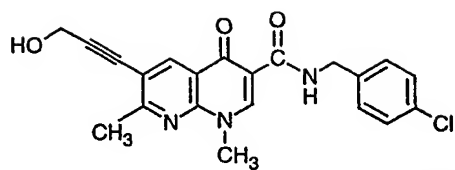


Compound No. 10

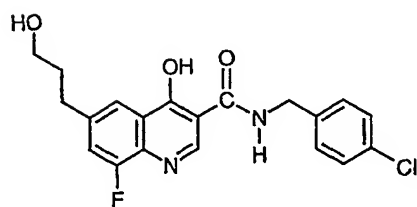
(Figure 1 continue)



(Figure 1 continue)

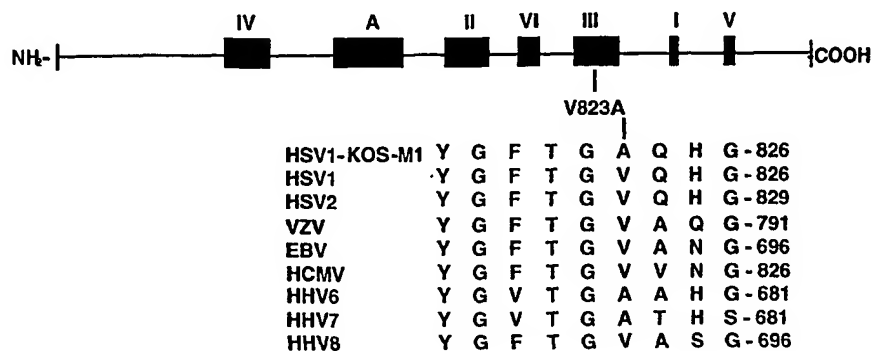


Compound No.15



Compound 17

Figure 2. The HSV1 (KOS Strain) DNA Polymerase Amino Acid 823 is Critical for Resistance to 4-Hydroxyquinolines and Related Compounds



Schematic of HSV1 polymerase illustrating the conserved regions A and I-VI found in class 2 polymerases. Also shown are the amino acid sequence for the highly conserved herpesvirus domain in region III which surrounds the HSV1 amino acid 823.

Figure 3 Serial Passage of HSV-1 in Presence of 20 μ M compound 17

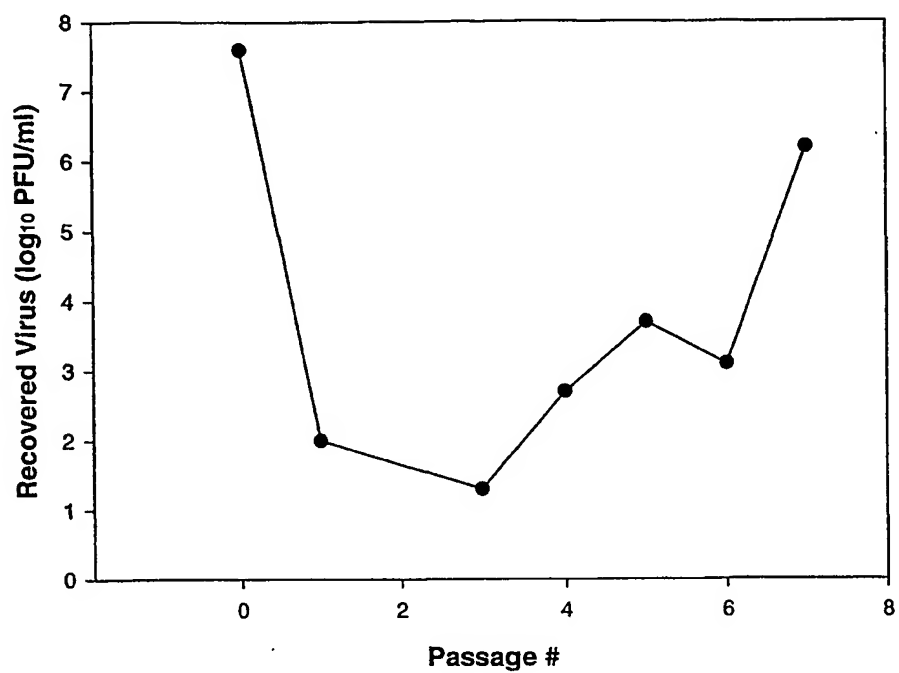


Figure 4 Comparison of Wild type HSV-1 and HSV-2 DNA Polymerases Amino Acid Sequences Alligned by Amino Acid Homology*

5	HSV2-MS	MFCAAGGPTS	PGGKSAARAA	SGFFAPHNPR	GATQTAPPPC	RRQNFYNPHL	-50
	HSV2-186	MFCAAGGPAS	PGGKSAARAA	SGFFAPHNPR	GATQTAPPPC	RRQNFYNPHL	-50
	HSV1-Kos	MFSGGGGPLS	PGGKSAARAA	SGFFAPAGPR	GAGR.GPPPC	LRQNFYNPYL	-49
	HSV1-Patton	MFSGGGGPLS	PGGKSAARAA	SGFFAPAGPR	GAGR.GPPPC	LRQNFYNPYL	-49
	HSV1-DJL	MFSGGGGPLS	PGGKSAARAA	SGFFAPAGPR	GAGR.GPPPC	LRQNFYNPYL	-49
10	HSV1-F	MFSGGGGPLS	PGGKSAARAA	SGFFAPAGPR	GAGR.GPPPC	LRQNFYNPYL	-49
	HSV2-MS	AQTGTQPKAP	GPAQRHTYYS	ECDEFRFIAP	RSLDEDAPAE	QRTGVHDGRL	-100
	HSV2-186	AQTGTQPKAP	GPAQRHTYYS	ECDEFRFIAP	RSLDEDAPAE	QRTGVHDGRL	-100
	HSV1-Kos	APVGTQQKPT	GPTQRHTYYS	ECDEFRFIAP	RVLDEDAPPE	KRAGVHDGHL	-99
	HSV1-Patton	APVGTQQKPT	GPTQRHTYYS	ECDEFRFIAP	RVLDEDAPPE	KRAGVHDGHL	-99
15	HSV1-DJL	APVGTQQKPT	GPTQRHTYYS	ECDEFRFIAP	RVLDEDAPPE	KRAGVHDGHL	-99
	HSV1-F	APVGTQQKPT	GPTQRHTYYS	ECDEFRFIAP	RVLDEDAPPE	KRAGVHDGHL	-99
20	HSV2-MS	RRAPKVYCGG	DERDVLRVGP	EGFWPRRLRL	WGGADHAPKG	FDPTVTVFHV	-150
	HSV2-186	RRAPKVYCGG	DERDVLRVGP	EGFWPRRLRL	WGGADHAPEG	FDPTVTVFHV	-150
	HSV-Kos	KRAPKVYCGG	DERDVLRVGS	GGFWPRRSRL	WGGVDHAPAG	FNPTVTVFHV	-149
	HSV1-Patton	KRAPKVYCGG	DERDVLRVGS	GGFWPRRSRL	WGGVDHAPAG	FNPTVTVFHV	-149
	HSV1-DJL	KRAPKVYCGG	DERDVLRVGS	GGFWPRRSRL	WGGVDHAPAG	FNPTVTVFHV	-149
25	HSV1-F	KRAPKVYCGG	DERDVLRVGS	GGFWPRRSRL	WGGVDHAPAG	FNPTVTVFHV	-149
	HSV2-MS	YDILEHVEHA	YSMRAAQLHE	RFMDAITPAG	TVITLLGLTP	EGHRVAVHVY	-200
	HSV2-186	YDILEHVEHA	YSMRAAQLHE	RFMDAITPAG	TVITLLGLTP	EGHRVAVHVY	-200
	HSV-Kos	YDILENVEHA	YGMRAAQFHA	RFMDAITPTG	TVITLLGLTP	EGHRVAVHVY	-199
	HSV1-Patton	YDILENVEHA	YGMRAAQFHA	RFMDAITPTG	TVITLLGLTP	EGHRVAVHVY	-199
30	HSV1-DJL	YDILENVEHA	YGMRAAQFHA	RFMDAITPTG	TVITLLGLTP	EGHRVAVHVY	-199
	HSV1-F	YDILENVEHA	YGMRAAQFHA	RFMDAITPTG	TVITLLGLTP	EGHRVAVHVY	-199
35	HSV2-MS	GTRQYFYMNK	AEVDRHLQCR	APRDL CERLA	AALRESPGAS	FRGISADHFE	-250
	HSV2-186	GTRQYFYMNK	AEVDRHLQCR	APRDL CERLA	AALRESPGAS	FRGISADHFE	-250
	HSV-Kos	GTRQYFYMNK	EEVDRHLQCR	APRDL CERMA	AALRESPGAS	FRGISADHFE	-249
	HSV1-Patton	GTRQYFYMNK	EEVDRHLQCR	APRDL CERMA	AALRESPGAS	FRGISADHFE	-249
	HSV1-DJL	GTRQYFYMNK	EEVDRHLQCR	APRDL CERMA	AALRESPGAS	FRGISADHFE	-249
40	HSV1-F	GTRQYFYMNK	EEVDRHLQCR	APRDL CERMA	AALRESPGAS	FRGISADHFE	-249
	HSV2-MS	AEVVERADVY	YYETRPTLYY	RVFVRSGRAL	AYLCDNF CPA	IRKYEGGVDA	-300
	HSV2-186	AEVVERADVY	YYETRPTLYY	RVFVRSGRAL	AYLCDNF CPA	IRKYEGGVDA	-300
	HSV-Kos	AEVVERTDVY	YYETRPALFY	RVYVRSGRVL	SYLCDNF CPA	IKKYEGGVDA	-299
	HSV1-Patton	AEVVERTDVY	YYETRPALFY	RVYVRSGRVL	SYLCDNF CPA	IKKYEGGVDA	-299
45	HSV1-DJL	AEVVERTDVY	YYETRPALFY	RVYVRSGRVL	SYLCDNF CPA	IKKYEGGVDA	-299
	HSV1-F	AEVVERTDVY	YYETRPALFY	RVYVRSGRVL	SYLCDNF CPA	IKKYEGGVDA	-299
50	HSV2-MS	TTRFILDNPG	FVTFGWYRLK	PGRGNAPAQP	RPPTAFGTSS	DVEFNCTADN	-350
	HSV2-186	TTRFILDNPG	FVTFGWYRLK	PGRGNAPAQP	RPPTAFGTSS	DVEFNCTADN	-350
	HSV-Kos	TTRFILDNPG	FVTFGWYRLK	PGRNNTLAQP	RAPMAFGTSS	DVEFNCTADN	-349
	HSV1-Patton	TTRFILDNPG	FVTFGWYRLK	PGRNNTLAQP	RAPMAFGTSS	DVEFNCTADN	-349
	HSV1-DJL	TTRFILDNPG	FVTFGWYRLK	PGRNNTLAQP	RAPMAFGTSS	DVEFNCTADN	-349
55	HSV1-F	TTRFILDNPG	FVTFGWYRLK	PGRNNTLAQP	RAPMAFGTSS	DVEFNCTADN	-349
	HSV2-MS	LAVEGAMCDL	PAYKLMCFDI	ECKAGGEDEL	AFPVAERPED	LVIQISCLLY	-400
	HSV2-186	LAVEGAMCDL	PAYKLMCFDI	ECKAGGEDEL	AFPVAERPED	LVIQISCLLY	-400
	HSV-Kos	LAIEGGMSDL	PAYKLMCFDI	ECKAGGEDEL	AFPVAGHPED	LVIQISCLLY	-399
	HSV1-Patton	LAIEGGMSDL	PAYKLMCFDI	ECKAGGEDEL	AFPVAGHPED	LVIQISCLLY	-399
60	HSV1-DJL	LAIEGGMSDL	PAYKLMCFDI	ECKAGGEDEL	AFPVAGHPED	LVIQISCLLY	-399
	HSV1-F	LAIEGGMSDL	PAYKLMCFDI	ECKAGGEDEL	AFPVAGHPED	LVIQISCLLY	-399
65	HSV2-MS	DLSTTALEHI	LLFSLGSCDL	PESHLSDLAS	RGLPAPVVLE	FDSEFEMLLA	-450
	HSV2-186	DLSTTALEHI	LLFSLGSCDL	PESHLSDLAS	RGLPAPVVLE	FDSEFEMLLA	-450
	HSV-Kos	DLSTTALEHV	LLFSLGSCDL	PESHNL ELAA	RGLPTPVVLE	FDSEFEMLLA	-449
	HSV1-Patton	DLSTTALEHV	LLFSLGSCDL	PESHNL ELAA	RGLPTPVVLE	FDSEFEMLLA	-449
	HSV1-DJL	DLSTTALEHV	LLFSLGSCDL	PESHNL ELAA	RGLPTPVVLE	FDSEFEMLLA	-449
70	HSV1-F	DLSTTALEHV	LLFSLGSCDL	PESHNL ELAA	RGLPTPVVLE	FDSEFEMLLA	-449

5	HSV2-MS	FMTFVKQYGP	EFVTGYNIIN	FDWPFVLTKL	TEIYKVPLDG	YGRMNNGRVF	-500
	HSV2-186	FMTFVKQYGP	EFVTGYNIIN	FDWPFVLTKL	TEIYKVPLDG	YGRMNNGRVF	-500
	HSV-Kos	FMTLVKQYGP	EFVTGYNIIN	FDWPFLLAKL	TDIYKVPLDG	YGRMNNGRVF	-499
	HSV1-Patton	FMTLVKQYGP	EFVTGYNIIN	FDWPFLLAKL	TDIYKVPLDG	YGRMNNGRVF	-499
	HSV1-DJL	FMTLVKQYGP	EFVTGYNIIN	FDWPFLLAKL	TDIYKVPLDG	YGRMNNGRVF	-499
	HSV1-F	FMTLVKQYGP	EFVTGYNIIN	FDWPFLLAKL	TDIYKVPLDG	YGRMNNGRVF	-499
10	HSV2-MS	RVWDIGQSHF	QKRSKIKNVG	MVNIDMYGII	TDKVKLSSYK	LNAVAEAVLK	-550
	HSV2-186	RVWDIGQSHF	QKRSKIKNVG	MVNIDMYGII	TDKVKLSSYK	LNAVAEAVLK	-550
	HSV-Kos	RVWDIGQSHF	QKRSKIKNVG	MVNIDMYGII	TDKIKLSSYK	LNAVAEAVLK	-549
	HSV1-Patton	RVWDIGQSHF	QKRSKIKNVG	MVNIDMYGII	TDKIKLSSYK	LNAVAEAVLK	-549
	HSV1-DJL	RVWDIGQSHF	QKRSKIKNVG	MVNIDMYGII	TDKIKLSSYK	LNAVAEAVLK	-549
	HSV1-F	RVWDIGQSHF	QKRSKIKNVG	MVNIDMYGII	TDKIKLSSYK	LNAVAEAVLK	-549
15	HSV2-MS	DKKKDLSYRD	IPAYYASGPA	QRGVIGEYCV	QDSLLVGQLF	FKFLPHLELS	-600
	HSV2-186	DKKKDLSYRD	IPAYYASGPA	QRGVIGEYCV	QDSLLVGQLF	FKFLPHLELS	-600
	HSV-Kos	DKKKDLSYRD	IPAYYAAGPA	QRGVIGEYCI	QDSLLVGQLF	FKFLPHLELS	-599
	HSV1-Patton	DKKKDLSYRD	IPAYYAAGPA	QRGVIGEYCI	QDSLLVGQLF	FKFLPHLELS	-599
	HSV1-DJL	DKKKDLSYRD	IPTYYAAGPA	QRGVIGEYCI	QDSLLVGQLF	FKFLPHLELS	-599
	HSV1-F	DKKKDLSYRD	IPAYYAAGPA	QRGVIGEYCI	QDSLLVGQLF	FKFLPHLELS	-599
25	HSV2-MS	AVARLAGINI	TRTIYDGOQI	RVFTCLLRLA	GQKGFILPDT	QGRFRGLDKE	-650
	HSV2-186	AVARLAGINI	TRTIYDGOQI	RVFTCLLRLA	GQKGFILPDT	QGRFRGLDKE	-650
	HSV-Kos	AVARLAGINI	TRTIYDGOQI	RVFTCLLRLA	DQKGFILPDT	QGRFRGAGGE	-649
	HSV1-Patton	AVARLAGINI	TRTIYDGOQI	RVFTCLLRLA	DQKGFILPDT	QGRFRGAGGE	-649
	HSV1-DJL	AVARLAGINI	TRTIYDGOQI	RVFTCLLRLA	DQKGFILPDT	QGRFRGAGGE	-649
	HSV1-F	AVARLAGINI	TRTIYDGOQI	RVFTCLLRLA	DQKGFILPDT	QGRFRGGGGE	-649
30	HSV2-MS	APKRPAVPRG	EGERPGDGNG	DEDKDDDE..	DEGDERE.E	VARETGGRHV	-697
	HSV2-186	APKRPAVPRG	EGERPGDGNG	DEDKDDDEDG	DEGDERE.E	VARETGGRHV	-697
	HSV-Kos	APKRPAARE	DEERP.....	EEGEDEDER	EEGGGEREPE	GARETAGRHV	-694
	HSV1-Patton	APKRPAARE	DEERP.....	EEGEDEDER	EEGGGEREPE	GARETAGRHV	-694
	HSV1-DJL	APKRPAARE	DEERP.....	EEGEDENER	EEGGGEREPE	GARETAGRHV	-694
	HSV1-F	APKRPAARE	DEERP.....	EEGEDEDER	EEGGGEREPE	GARETAGRHV	-694
35	HSV2-MS	GYQGARVLDP	TSGFHVDPVV	VDFASLYPS	IIQAHNLCFS	TLSLRPEAVA	-747
	HSV2-186	GYQGARVLDP	TSGFHVDPVV	VDFASLYPS	IIQAHNLCFS	TLSLRPEAVA	-749
	HSV-Kos	GYQGARVLDP	TSGFHVNPVV	VDFASLYPS	IIQAHNLCFS	TLSLRADAVA	-744
	HSV1-Patton	GYQGARVLDP	ISGFHVNPVV	VDFASLYPS	IIQAHNLCFS	TLSLRADAVA	-744
	HSV1-DJL	GYQGARVLDP	TSGFHVNPVV	VDFASLYPS	IIQAHNLCFS	TLSLRADAVA	-744
	HSV1-F	GYQGARVLDP	TSGFHVNPVV	VDFASLYPS	IIQAHNLCFS	TLSLRADAVA	-744
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	HSV2-186	HLEADR DYLE	IEVGRRRLFF	VKAHVRESLL	SILLRDWLAM	RKQIRSRIPQ	-799
	HSV-Kos	HLEAGKDYLE	IEVGRRRLFF	VKAHVRESLL	SILLRDWLAM	RKQIRSRIPQ	-794
	HSV1-Patton	HLEAGKDYLE	IEVGRRRLFF	VKAHVRESLL	SILLRDWLAM	RKQIRSRIPQ	-794
	HSV1-DJL	HLEAGKDYLE	IEVGRRRLFF	VKAHVRESLL	SILLRDWLAM	RKQIRSRIPQ	-794
	HSV1-F	HLEAGKDYLE	IEVGRRRLFF	VKAHVRESLL	SILLRDWLAM	RKQIRSRIPQ	-794
50	HSV2-MS	SPPEEAVLLD	KQQAIAKVVC	NSVYGFTGVQ	HGLLPCLHVA	ATVTTIGREM	-847
	HSV2-186	SPPEEAVLLD	KQQAIAKVVC	NSVYGFTGVQ	HGLLPCLHVA	ATVTTIGREM	-849
	HSV-Kos	SPPEEAVLLD	KQQAIAKVVC	NSVYGFTGVQ	HGLLPCLHVA	ATVTTIGREM	-844
	HSV1-Patton	SPPEEAVLLD	KQQAIAKVVC	NSVYGFTGVQ	HGLLPCLHVA	ATVTTIGREM	-844
	HSV1-DJL	SPPEEAVLLD	KQQAIAKVVC	NSVYGFTGVQ	HGLLPCLHVA	ATVTTIGREM	-844
	HSV1-F	SPPEEAVLLD	KQQAIAKVVC	NSVYGFTGVQ	HGLLPCLHVA	ATVTTIGREM	-844
60	HSV2-MS	LLATRAYVHA	RWAEFDQLLA	DFPEAAGMRA	PGPYSMRIIY	GDTSIFVLC	-897
	HSV2-186	LLATRAYVHA	RWAEFDQLLA	DFPEAAGMRA	PGPYSMRIIY	GDTSIFVLC	-899
	HSV-Kos	LLATREYVHA	RWAAFEQLLA	DFPEAADMRA	PGPYSMRIIY	GDTSIFVLC	-894
	HSV1-Patton	LLATREYVHA	RWAAFEQLLA	DFPEAADMRA	PGPYSMRIIY	GDTSIFVLC	-894
	HSV1-DJL	LLATREYVHA	RWAAFEQLLA	DFPEAADMRA	PGPYSMRIIY	GDTSIFVLC	-894
	HSV1-F	LLATREYVHA	RWAAFEQLLA	DFPEAADMRA	PGPYSMRIIY	GDTSIFVLC	-894
65	HSV2-MS	RGLTAAGLVA	MGDKMASHIS	RALFLPPIKL	ECEKTFTKLL	LIAKKKYIGV	-947
	HSV2-186	RGLTAAGLVA	MGDKMASHIS	RALFLPPIKL	ECEKTFTKLL	LIAKKKYIGV	-949
	HSV-Kos	RGLTAAGLTA	MGDKMASHIS	RALFLPPIKL	ECEKTFTKLL	LIAKKKYIGV	-944
	HSV1-Patton	RGLTAAGLTA	MGDKMASHIS	RALFLPPIKL	ECEKTFTKLL	LIAKKKYIGV	-944

	HSV1-DJL	RGLTAAGLTA	VGDKMASHIS	RALFLPPIKL	ECEKTFTKLL	LIAKKKYIGV	-944
	HSV1-F	RGLTAAGLTA	VGDKMASHIS	RALFLSPIKL	ECEKTFTKLL	LIAKKKYIGV	-944
5	HSV2-MS	ICGGKMLIKG	VDLVRKNNCA	FINRTSRALV	DLLFYDDTVS	GAAAALAERP	-997
	HSV2-186	ICGGKMLIKG	VDLVRKNNCA	FINRTSRALV	DLLFYDDTVS	GAAAALAERP	-999
	HSV-Kos	IYGGKMLIKG	VDLVRKNNCA	FINRTSRALV	DLLFYDDTVS	GAAAALAERP	-994
	HSV1-Patton	IYGGKMLIKG	VDLVRKNNCA	FINRTSRALV	DLLFYDDTVS	GAAAALAERP	-994
	HSV1-DJL	IYGGKMLIKG	VDLVRKNNCA	FINRTSRALV	DLLFYDDTVS	GAAAALAERP	-994
10	HSV1-F	IYGGKMLIKG	VDLVRKNNCA	FINRTSRALV	DLLFYDDTVS	GAAAALAERP	-994
	HSV2-MS	AEWLARPLP	EGLQAFGAVL	VDAHRRITDP	ERDIQDFVLT	AELSRHPRAY	-1047
	HSV2-186	AEWLARPLP	EGLQAFGAVL	VDAHRRITDP	ERDIQDFVLT	AELSRHPRAY	-1049
	HSV-Kos	AEWLARPLP	EGLQAFGAVL	VDAHRRITDP	ERDIQDFVLT	AELSRHPRAY	-1044
	HSV1-Patton	AEWLARPLP	EGLQAFGAVL	VDAHRRITDP	ERDIQDFVLT	AELSRHPRAY	-1044
15	HSV1-DJL	AEWLARPLP	EGLQAFGAVL	VDAHRRITDP	ERDIQDFVLT	AELSRHPRAY	-1044
	HSV1-F	AEWLARPLP	EGLQAFGAVL	VDAHRRITDP	ERDIQDFVLT	AELSRHPRAY	-1044
20	HSV2-MS	TNKRLAHLTV	YYKLMARRAQ	VPSIKDRIPY	VIVAQTREVE	ETVARLAALR	-1097
	HSV2-186	TNKRLAHLTV	YYKLMARRAQ	VPSIKDRIPY	VIVAQTREVE	ETVARLAALR	-1099
	HSV-Kos	TNKRLAHLTV	YYKLMARRAQ	VPSIKDRIPY	VIVAQTREVE	ETVARLAALR	-1094
	HSV1-Patton	TNKRLAHLTV	YYKLMARRAQ	VPSIKDRIPY	VIVAQTREVE	ETVARLAALR	-1094
	HSV1-DJL	TNKRLAHLTV	YYKLMARRAQ	VPSIKDRIPY	VIVAQTREVE	ETVARLAALR	-1094
25	HSV1-F	TNKRLAHLTV	YYKLMARRAQ	VPSIKDRIPY	VIVAQTREVE	ETVARLAALR	-1094
	HSV2-MS	ELDAAAPGDE	PAPPAALPSP	AKRPRETPSH	ADPPGGASKP	RKLLVSELA	-1147
	HSV2-186	ELDAAAPGDE	PAPPAALPSP	AKRPRETPSH	ADPPGGASKP	RKLLVSELA	-1149
	HSV-Kos	ELDAAAPGDE	PAPPAALPSP	AKRPRETPSH	ADPPGGASKP	RKLLVSELA	-1144
	HSV1-Patton	ELDAAAPGDE	PAPPAALPSP	AKRPRETPSP	ADPPGGASKP	RKLLVSELA	-1144
30	HSV1-DJL	ELDAAAPGDE	PAPPAALPSP	AKRPRETPSP	ADPPGGASKP	RKLLVSELA	-1144
	HSV1-F	ELDAAAPGDE	PAPPAALPSP	AKRPRETPLH	ADPPGGASKP	RKLLVSELA	-1144
35	HSV2-MS	DPGYAIARGV	PLNTDYYFSH	LLGAACVTFK	ALFGNNAKIT	ESLLKRFIPE	-1197
	HSV2-186	DPGYAIARGV	PLNTDYYFSH	LLGAACVTFK	ALFGNNAKIT	ESLLKRFIPE	-1199
	HSV-Kos	DPAYAIAHGV	ALNTDYYFSH	LLGAACVTFK	ALFGNNAKIT	ESLLKRFIPE	-1194
	HSV1-Patton	DPAYAIAHGV	ALNTDYYFSH	LLGAACVTFK	ALFGNNAKIT	ESLLKRFIPE	-1194
	HSV1-DJL	DPAYAIAHGV	ALNTDYYFSH	LLGAACVTFK	ALFGNNAKIT	ESLLKRFIPE	-1194
40	HSV1-F	DPAYAIAHGV	ALNTDYYFSH	LLGAACVTFK	ALFGNNAKIT	ESLLKRFIPE	-1194
	HSV2-MS	TWHPDDVAA	RLRAAGFGPA	GAGATAEETR	RMLHRAFDTL	A*	-1238
	HSV2-186	TWHPDDVAA	RLRAAGFGPA	GAGATAEETR	RMLHRAFDTL	A*	-1240
	HSV-Kos	VWHPDDVAA	RLRAAGFGAV	GAGATAEETR	RMLHRAFDTL	A*	-1235
	HSV1-Patton	VWHPDDVTA	RLRAAGFGAV	GAGATAEETR	RMLHRAFDTL	A*	-1235
45	HSV1-DJL	VWHPDDVAA	RLRTAGFGAV	GAGATAEETR	RMLHRAFDTL	A*	-1235
	HSV1-F	VWHPDDVAA	RLRAAGFGAV	GAGATAEETR	RMLHRAFDTL	A*	-1235

*Amino acid alignment demonstrates difference in amino acid's sequences.

*The gaps "....." indicate missing amino acids relative to other stanins.

*Wild HSV2-MS is listed as SEQ. ID NO 14.

*Wild HSV2-186 is listed as SEQ. ID NO 15.

50 *Wild HSV-Kos is listed as SEQ. ID NO 16.

*Wild HSV1-Patton is listed as SEQ. ID NO 17.

*Wild HSV1-DJL is listed as SEQ. ID NO 18.

*Wild HSV1-F is listed as SEQ. ID NO 19.

Figure 5 DNA and amino acid sequence list**SEQ. ID. NO. 1 DNA sequence of DNA polymerase gene for HSV2-MS-M1**

5 1 ATGTTTGTG CCGCGGGCGG CCCGACTTCC CCCGGGGGGA AGTCGGCGGC
 51 TCGGGCGGCG TCTGGGTTTT TTGCCCCCA CAACCCCGG GGAGCCACCC
 10 101 AGACGGCACC GCCGCTTGC CGCCGGCAGA ACTTCTACAA CCCCCACCTC
 151 GCTCAGACCG GAACGCAGCC AAAGGCCCCC GGGCCGGCTC AGCGCCATAC
 201 GTACTACAGC GAGTGCAGC AATTTCGATT TATCGCCCCG CGTTCGCTGG
 15 251 ACGAGGACGC CCCC GCGGAG CAGCGCACC GGTCCACGA CGGCCGCTC
 301 CGGCGCGCCC CTAAGGTGTA CTGCGGGGGG GACGAGCGCG ACGTCCTCCG
 351 CGTGGGCCCC GAGGGCTTCT GGCCGCGTCG CTTGCGCCTG TGGGGCGGTG
 20 401 CGGACCATGC CCCCAAGGGG TTCGACCCA CCGTCACCGT CTTCCACGTG
 451 TACGACATCC TGGAGCACGT GGAACACGCG TACAGCATGC GCGCCGCCCA
 25 501 GCTCCACGAG CGATTTATGG ACGCCATCAC GCCC GCCGGG ACCGTCATCA
 551 CGCTTCTGGG TCTGACCCCC GAAGGCCATC GCGTCGCCGT TCACGTCTAC
 601 GGCACGCGGC AGTACTTTTA CATGAACAAG GCGGAGGTGG ATCGGCACCT
 30 651 GCAGTGCCGT GCCCCGCGCG ATCTCTGCGA GCGCCTGGCG GCGGCCCTGC
 701 GCGAGTCGCC GGGGGCGTCG TTCCGCGGCA TCTCCGCGGA CCACTTCGAG
 35 751 GCGGAGGTGG TGGAGCGCGC CGACGTGTAC TATTACGAAA CGCGCCCGAC
 801 CCTGTACTAC CGCGTCTTCG TGCGAAGCGG GCGCGCGCTG GCCTACCTGT
 851 GCGACAACTT TTGCCCCGCG ATCAGGAAGT ACGAGGGGGG CGTCGACGCC
 40 901 ACCACCCGGT TTATCCTGGA CAACCCGGGG TTTGTACCT TCGGCTGGTA
 951 CCGCCTCAAG CCCGGCCGCG GGAACGCGCC GGCCCAACCG CGCCCCCGA
 45 1001 CGGCGTTTCGG AACCTCGAGC GACGTCGAGT TTAAGTGCAC GGCGGACAAC
 1051 CTGGCCGTCG AGGGGGCCAT GTGTGACCTG CCGGCCTACA AGCTCATGTG
 1101 CTTCGATATC GAATGCAAGG CCGGGGGGGA GGACGAGCTG GCCTTTCCGG
 50 1151 TCGCGGAACG CCCGGAAGAC CTCGTCATCC AGATCTCCTG TCTGCTCTAC
 1201 GACCTGTCCA CCACCGCCCT CGAGCACATC CTCCTGTTTT CGCTCGGATC
 55 1251 CTGCGACCTC CCCGAGTCCC ACCTCAGCGA TCTCGCCTCC AGGGGCCTGC
 1301 CGGCCCCCGT CGTCCTGGAG TTTGACAGCG AATTCGAGAT GCTGCTGGCC

1351 TTCATGACCT TCGTCAAGCA GTACGGCCCC GAGTTCGTGA CCGGGTACAA
1401 CATCATCAAC TTCGACTGGC CCTTCGTCCT GACCAAGCTG ACGGAGATCT
5 1451 ACAAGGTCCC GCTCGACGGG TACGGGCGCA TGAACGGCCG GGGTGTGTTC
1501 CGCGTGTGGG ACATCGGCCA GAGCCACTTT CAGAAGCGCA GCAAGATCAA
1551 GGTGAACGGG ATGGTGAACA TCGACATGTA CGGCATCATC ACCGACAAGG
10 1601 TCAAACCTCTC CAGCTACAAG CTGAACGCCG TCGCCGAGGC CGTCTTGAAG
1651 GACAAGAAGA AGGATCTGAG CTACCGCGAC ATCCCCGCCT ACTACGCCTC
15 1701 CGGGCCCCGCG CAGCGCGGGG TGATCGGCGA GTATTGTGTG CAGGACTCGC
1751 TGCTGGTCGG GCAGCTGTTC TTCAAGTTTC TGCCGCACCT GGAGCTTTCC
1801 GCCGTCGCGC GCCTGGCGGG CATCAACATC ACCCGCACCA TCTACGACGG
20 1851 CCAGCAGATC CGCGTCTTCA CGTGCCTCCT GCGCCTTGCG GGCCAGAAGG
1901 GCTTCATCCT GCCGGACACC CAGGGGCGGT TTCGGGGCCT CGACAAGGAG
25 1951 GCGCCCAAGC GCCCGGCCGT GCCTCGGGGG GAAGGGGAGC GGCCGGGGGA
2001 CGGGAACGGG GACGAGGATA AGGACGACGA CGAGGACGAG GACGGGGACG
2051 AGCGCGAGGA GGTCGCGCGC GAGACCGGGG GCCGGCACGT TGGGTACCAG
30 2101 GGGGCCCCGG TCCTCGACCC CACCTCCGGG TTTCACGTCG ACCCCGTGGT
2151 GGTGTTTGAC TTGCCAGCC TGTACCCAG CATCATCCAG GCCACAACC
35 2201 TGTGCTTCAG TACGCTCTCC CTGCGGCCCC AGGCCGTCG GCACCTGGAG
2251 GCGGACCGGG ACTACCTGGA GATCGAGGTG GGGGGCCGAC GGCTGTTCTT
2301 CGTGAAGGCC CACGTACGCG AGAGCCTGCT GAGCATCCTG CTGCGCGACT
40 2351 GGCTGGCCAT GCGAAAGCAG ATCCGCTCGC GGATCCCCCA GAGCACCCCC
2401 GAGGAGGCCG TCCTCCTCGA CAAGCAACAG GCCGCCATCA AGGTGGTGTG
45 2451 CAACTCGGTG TACGGGTTCA CCGGGGCGCA GCACGGTCTT CTGCCCTGCC
2501 TGCACGTGGC CGCCACCGTG ACGACCATCG GCCGCGAGAT GCTCCTCGCG
2551 ACGCGCGCGT ACGTGCACGC GCGCTGGGCG GAGTTCGATC AGCTGCTGGC
50 2601 CGACTTTCCG GAGGCGGCCG GCATGCGCGC CCCCAGTCCG TACTCCATGC
2651 GCATCATCTA CGGGGACACG GACTCCATTT TCGTTTTGTG CCGCGGCCTC
55 2701 ACGGCCGCGG GCCTGGTGGC CATGGGCGAC AAGATGGCGA GCCACATCTC
2751 GCGCGCGCTG TTCCTCCCCC CGATCAAGCT CGAGTGCGAA AAAACGTTCA
2801 CCAAGCTGCT GTCATCGCC AAGAAAAAGT ACATCGGCGT CATCTGCGGG
60

2851 GGCAAGATGC TCATCAAGGG CGTGGATCTG GTGCGCAAAA ACAACTGCGC
2901 GTTTATCAAC CGCACCTCCA GGGCCCTGGT CGACCTGCTG TTTTACGACG
5 2951 ATACCGTATC CGGAGCGGCC GCCGCGTTAG CCGAGCGCCC CGCAGAGGAG
3001 TGGCTGGCGC GACCCCTGCC CGAGGGACTG CAGGCGTTCG GGGCCGTCCT
3051 CGTAGACGCC CATCGGCGCA TCACCGACCC GGAGAGGGAC ATCCAGGACT
10 3101 TTGTCCTCAC CGCCGAACTG AGCAGACACC CGCGCGCGTA CACCAACAAG
3151 CGCCTGGCCC ACCTGACGGT GTATTACAAG CTCATGGCCC GCCGCGCGCA
15 3201 GGTCCCGTCC ATCAAGGACC GGATCCCGTA CGTGATCGTG GCCCAGACCC
3251 GCGAGGTAGA GGAGACGGTC GCGCGGCTGG CCGCCCTCCG CGAGCTAGAC
3301 GCCGCCGCCC CAGGGGACGA GCCCGCCCCC CCAGCGGCCC TGCCCTCCCC
20 3351 GGCCAAGCGC CCCCAGGAGA CGCCGTCGCA TGCCGACCCC CCGGGAGGCG
3401 CGTCCAAGCC CCGCAAGCTG CTGGTGTCCG AGCTGGCGGA GGATCCCGGG
25 3451 TACGCCATCG CCCGGGGCGT TCCGCTCAAC ACGGACTATT ACTTCTCGCA
3501 CCTGCTGGGG GCGGCCTGCG TGACGTTCAA GGCCCTGTTT GGAAATAACG
3551 CCAAGATCAC CGAGAGTCTG TTAAAGAGGT TTATTCCCGA GACGTGGCAC
30 3601 CCCCCGACG ACGTGGCCGC GCGGCTCAGG GCCGCGGGGT TCGGGCCGGC
3651 GGGGGCCGGC GCTACGGCGG AGGAACTCG TCGAATGTTG CATAGAGCCT
35 3701 TTGATACTCT AGCATGA

SEQ. ID. NO. 2 Amino acid sequence of DNA polymerase for HSV2-MS-M1

1 MFCAAGGPTS PGGKSAARAA SGFFAPHNPR GATQTAPPPC RRQNFYNPHL
5 51 AQTGTQPKAP GPAQRHTYYS ECDEFRLFAP RSLDEDAPAE QRTGVHDGRL
101 RRAPKVYCGG DERDVLRVGP EGFWRRLRL WGGADHAPKG FDPTVTVFHV
151 YDILEHVEHA YSMRAAQLHE RFMDAITPAG TVTLLGLTP EGHRAVAVHVY
10 201 GTRQYFYMNK AEVDRHLQCR APRDLCERLA AALRESPGAS FRGISADHFE
251 AEVVERADV YETRPTLYY RVFVRSGRAL AYLCDNFCPA IRKYEGGVDA
15 301 TTRFILDNPG FVTFGWYRLK PGRGNAPAQ RPPTAFGTSS DVEFNCTADN
351 LAVEGAMCDL PAYKLMCFDI ECKAGGEDEL AFPVAERPED LVIQISCLLY
401 DLSTTALEHI LLFSLGSCDL PESHLSDLAS RGLPAPVVLE FDSEFEMLLA
20 451 FMTFVKQYGP EFVTGYNIN FDWPFVLTCL TEIYKVPLDG YGRMNRRGVF
501 RVWDIGQSHF QKRSKIKVNG MVNIDMYGH TDKVKLSSYK LNAVAEAVLK
25 551 DKKKDLSDYRD IPAYYASGPA QRGVIGEYCV QDSSLVGQLF FKFLPHLELS
601 AVARLAGINI TRTIYDQQI RVFTCLRLA GQKGFILPDT QGRFRGLDKE
651 APKRPAVPRG EGERPGDGNG DEDKDDDEDE DGDEREEVAR ETGGRHVGYYQ
30 701 GARVLDPTSG FHVDPVVVD FASLYPSIIQ AHNLCFSTLS LRPEAVAHLE
751 ADRDYLEIEV GGRRLFFVKA HVRESLLSIL LRDWLAMRKQ IRSRIPQSTP
35 801 EEAVLLDKQQ AAIKVVNSV YGFTGAQHGL LPCLHVAATV TTIGREMLLA
851 TRAYVHARWA EFDQLLADFP EAAGMRAPGP YSMRIYGDY DSIFVLCRGL
901 TAAGLVAMGD KMASHISRAL FLPIKLECE KTFTKLLLIA KKKYIGVICG
40 951 GKMLIKGVDL VRKNNCAFIN RTSRALVDLL FYDDTVSGAA AALAERPAAE
1001 WLARPLPEGL QAFGAVLVDA HRRITDPERD IQDFVLTAE SRHPRAYTNK
45 1051 RLAHLTVYYK LMARRAQVPS IKDRIPYVIV AQTREVEETV ARLAALRELD
1101 AAAPGDEPAP PAALPSAKR PRETPSHADP PGGASKPRKL LVSELAEDPG
1151 YAIARGVPLN TDYYFSHLLG AACVTFKALF GNNAKITESL LKRFIPETWH
50 1201 PPDDVAARLR AAGFGPAGAG ATAETRRML HRAFDTLA*

SEQ.ID.NO. 3 DNA sequence of DNA polymerase gene for HSV2-186-M1

1 ATGTTTTGTG CCGCGGGCGG CCCGGCTTCC CCCGGGGGGA AGTCGGCGGC
5 51 TCGGGCGGCG TCTGGGTTTT TTGCCCCCA CAACCCCGG GGAGCCACCC
101 AGACGGCACC GCCGCCTTGC CGCCGGCAGA ACTTCTACAA CCCCCACCTC
151 GCTCAGACCG GAACGCAGCC AAAGGCCCCC GGGCCGGCTC AGCGCCATAC
10 201 GTACTACAGC GAGTGCGACG AATTTCGATT TATCGCCCCG CGTTCGCTGG
251 ACGAGGACGC CCCC GCGGAG CAGCGCACCG GGGTCCACGA CGGCCGCCTC
15 301 CGGCGCGCCC CTAAGGTGTA CTGCGGGGGG GACGAGCGCG ACGTCCTCCG
351 CGTGGGCCCC GAGGGCTTCT GGCCGCGTCG CTTGCGCCTG TGGGGCGGTG
401 CGGACCATGC CCCC GAGGGG TTCGACCCA CCGTCACCGT CTTCCACGTG
20 451 TACGACATCC TGGAGCACGT GGAACACGCG TACAGCATGC GCGCCGCCCA
501 GCTCCACGAG CGATTTATGG ACGCCATCAC GCCCGCCGGG ACCGTCATCA
25 551 CGCTTCTGGG TCTGACCCCC GAAGGCCATC GCGTCGCCGT TCACGTCTAC
601 GGCACGCGGC AGTACTTTTA CATGAACAAG GCGGAGGTGG ATCGGCACCT
651 GCAGTGCCGT GCCCCGCGCG ATCTCTGCGA GCGCCTGGCG GCGGCCCTGC
30 701 GCGAGTCGCC GGGGGCGTCG TTCCGCGGCA TCTCCGCGGA CCACTTCGAG
751 GCGGAGGTGG TGGAGCGCGC CGACGTGTAC TATTACGAAA CGCGCCCGAC
35 801 CCTGTACTAC CGCGTCTTCG TCGGAAGCGG GCGCGCGCTG GCCTACCTGT
851 GCGACAACCT TTGCCCCGCG ATCAGGAAGT ACGAGGGGGG CGTCGACGCC
901 ACCACCCGGT TTATCCTGGA CAACCCGGGG TTTGTACCT TCGGCTGGTA
40 951 CCGCCTCAAG CCCGGCCGCG GGAACGCGCC GGCCCAACCG CGCCCCCGA
1001 CGGCGTTCGG AACCTCGAGC GACGTCGAGT TAACTGCAC GCGGACAAC
45 1051 CTGGCCGTCG AGGGGGCCAT GTGTGACCTG CCGGCCTACA AGCTCATGTG
1101 CTTGATATC GAATGCAAGG CCGGGGGGGA GGACGAGCTG GCCTTTCCGG
1151 TCGCGGAACG CCCGGAAGAC CTCGTCATCC AGATCTCCTG TCTGCTCTAC
50 1201 GACCTGTCCA CCACCGCCCT CGAGCACATC CTCCTGTTTT CGCTCGGATC
1251 CTGCGACCTC CCCGAGTCCC ACCTCAGCGA TCTCGCCTCC AGGGGCCTGC
55 1301 CGGCCCCCGT CGTCCTGGAG TTTGACAGCG AATTCGAGAT GCTGCTGGCC
1351 TTCATGACCT TCGTCAAGCA GTACGGCCCC GAGTTCGTGA CCGGGTACAA
1401 CATCATCAAC TCGACTGGC CCTTCGTCCT GACCAAGCTG ACGGAGATCT
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1451 ACAAGGTCCC GCTCGACGGG TACGGGCGCA TGAACGGCCG GGGTGTGTTC
1501 CGCGTGTGGG ACATCGGCCA GAGCCACTTT CAGAAGCGCA GCAAGATCAA
5 1551 GGTGAACGGG ATGGTGAACA TCGACATGTA CGGCATCATC ACCGACAAGG
1601 TCAAACCTCTC CAGCTACAAG CTGAACGCCG TCGCCGAGGC CGTCTTGAAG
1651 GACAAGAAGA AGGATCTGAG CTACCGCGAC ATCCCCGCCT ACTACGCCTC
10 1701 CGGGCCCCGCG CAGCGCGGGG TGATCGGCCA GTATTGTGTG CAGGACTCGC
1751 TGCTGGTCGG GCAGCTGTTC TTCAAGTTTC TGCCGCACCT GGAGCTTTCC
1801 GCCGTCGCGC GCCTGGCGGG CATCAACATC ACCCGCACCA TCTACGACGG
1851 CCAGCAGATC CGCGTCTTCA CGTGCCTCCT GCGCCTTGCG GGCCAGAAGG
1901 GCTTCATCCT GCCGGACACC CAGGGGCGGT TTCGGGGCCT CGACAAGGAG
20 1951 GCGCCCAAGC GCGCGGCCGT GCCTCGGGGG GAAGGGGAGC GGCCGGGGGA
2001 CGGGAACGGG GACGAGGATA AGGACGACGA CGAGGACGGG GACGAGGACG
2051 GGGACGAGCG CGAGGAGGTC GCGCGCGAGA CCGGGGGCCG GCACGTTGGG
2101 TACCAGGGGG CCCGGGTCCT CGACCCACC TCCGGGTTTC ACGTCGACCC
2151 CGTGGTGGTG TTTGACTTTG CCAGCCTGTA CCCCAGCATC ATCCAGGCCC
30 2201 ACAACCTGTG CTTCAGTACG CTCTCCCTGC GGCCGAGGC CGTCGCGCAC
2251 CTGGAGGCGG ACCGGGACTA CCTGGAGATC GAGGTGGGGG GCCGACGGCT
2301 GTTCTTCGTG AAGGCCACG TACGCGAGAG CCTGCTGAGC ATCCTGCTGC
2351 GCGACTGGCT GGCCATGCGA AAGCAGATCC GCTCGCGGAT CCCCCAGAGC
2401 CCCCCGAGG AGGCCGTCCT CCTCGACAAG CAACAGGCCG CCATCAAGGT
40 2451 GGTGTGCAAC TCGGTGTACG GGTTCACCGG GGCGCAGCAC GGTCTTCTGC
2501 CCTGCCTGCA CGTGGCCGCC ACCGTGACGA CCATCGGCCG CGAGATGCTC
2551 CTCGCGACGC GCGCGTACGT GCACGCGCGC TGGGCGGAGT TCGATCAGCT
2601 GCTGGCCGAC TTTCCGGAGG CGGCCGGCAT GCGCGCCCCC GGTCCGTACT
2651 CCATGCGCAT CATCTACGGG GACACGGACT CCATTTTCGT TTTGTGCCGC
50 2701 GGCCTCACGG CCGCGGGCCT GGTGGCCATG GGCGACAAGA TGGCGAGCCA
2751 CATCTCGCGC GCGCTGTTCC TCCCCCGAT CAAGCTCGAG TGCGAAAAAA
2801 CGTTCACCAA GCTGCTGCTC ATCGCCAAGA AAAAGTACAT CGGCGTCATC
2851 TGCGGGGGCA AGATGCTCAT CAAGGGCGTG GATCTGGTGC GCAAAAACAA
2901 CTGCGCGTTT ATCAACCGCA CCTCCAGGGC CCTGGTCGAC CTGCTGTTTT
60

2951 ACGACGATAC CGTATCCGGA GCGGCCGCCG CGTTAGCCGA GCGCCCCGCA
3001 GAGGAGTGGC TGGCGCGACC CCTGCCCGAG GGA CTGCAGG CGTTCGGGGC
5 3051 CGTCCTCGTA GACGCCCATC GGCGCATCAC CGACCCGGAG AGGGACATCC
3101 AGGACTTTGT CCTCACCGCC GAACTGAGCA GACACCCGCG CGCGTACACC
3151 AACAAAGCGCC TGGCCCACCT GACGGTGTAT TACAAGCTCA TGGCCCCGCCG
10 3201 CGCGCAGGTC CCGTCCATCA AGGACCGGAT CCCGTACGTG ATCGTGGCCC
3251 AGACCCGCGA GGTAGAGGAG ACGGTCGCGC GGCTGGCCGC CCTCCGCGAG
15 3301 CTAGACGCCG CCGCCCCAGG GGACGAGCCC GGGCCCCCAG CGGCCCTGCC
3351 CTCCCCGGCC AAGCGCCCCC GGGAGACGCC GTCGCATGCC GACCCCCCGG
3401 GAGGCGCGTC CAAGCCCCGC AAGCTGCTGG TGTCCGAGCT GGC GGAGGAT
20 3451 CCCGGGTACG CCATCGCCCC GGGCGTTCCG CTCAACACGG ACTATTACTT
3501 CTCGCACCTG CTGGGGGCGG CCTGCGTGAC GTTCAAGGCC CTGTTTGGAA
25 3551 ATAACGCCAA GATCACCGAG AGTCTGTAA AGAGGTTTAT TCCCGAGACG
3601 TGGCACCCCC CGGACGACGT GGCCGCGCGG CTCAGGGCCG CGGGGTTTCGG
3651 GCCGGCGGGG GCCGGCGCTA CGGCGGAGGA AACTCGTCGA ATGTTGCATA
30 3701 GAGCCTTTGA TACTCTAGCA TGA

SEQ.ID.NO. 4 Amino acid sequence of DNA polymerase for HSV2-186-M1

5 1 MFCAAGGPAS PGGKSAARAA SGFFAPHNPR GATQTAPPPC RRQNFYNPHL
51 AQTGTQPKAP GPAQRHTYYS ECDEFRIAP RSLDEDAPAE QRTGVHDGRL
101 RRAPKVYCGG DERDVLRVGP EGFWRRLRL WGGADHAPEG FDPTVTVFHV
10 151 YDILEHVEHA YSMRAAQLHE RFMDAITPAG TVITLLGLTP EGHRAVHVY
201 GTRQYFYMNK AEVDRHLQCR APRDLCERLA AALRESPGAS FRGISADHFE
15 251 AEVVERADVY YYETRPTLYY RVFVRSGRAL AYLCDNFCPA IRKYEGGVDA
301 TTRFILDNPG FVTFGWYRLK PGRGNAPAQP RPPTAFGTSS DVEFNCTADN
351 LAVEGAMCDL PAYKLMCFDI ECKAGGEDEL AFPVAERPED LVIQISCLLY
20 401 DLSTTALEHI LLFSLGSCDL PESHLSDLAS RGLPAPVVLE FDSEFEMLLA
451 FMTFVKQYGP EFVTGYNIN FDWPFVLTKL TEIYKVPLDG YGRMNNGRGVF
25 501 RVWDIGQSHF QKRSKIKVNG MVNIDMYGII TDKVKLSSYK LNAVAEAVLK
551 DKKKDLSYRD IPAYYASGPA QRGVIGEYCV QDSSLVGQLF FKFLPHLELS
601 AVARLAGINI TRTTYDGQOI RVFTCLRLA GQKGFILPDT QGRFRGLDKE
30 651 APKRAVPRG EGERPGDGNG DEDKDDDEDG DEDGDEREEV ARETGGRHVG
701 YQGARVLDPT SGFHVDPVVV FDFASLYPSI IQAHNLCFST LSLRPEAVAH
35 751 LEADRDYLEI EVGGRRLFFV KAHVRESLLS ILLRDWLAMR KQIRSRI PQS
801 PPEEAVLLDK QQAAIKVVCN SVYGFTGAQH GLLPCLHVAA TVTTIGREML
851 LATRAYVHAR WAEFDQLLAD FPEAAGMRAP GPYSMRIYG DTDSIFVLCR
40 901 GLTAAGLVAM GDKMASHISR ALFLPPIKLE CEKTFKLLL IAKKKYIGVI
951 CGGKMLIKGV DLVRKNNCAF INRTSRALVD LLFYDDTVSG AAAALAERPA
45 1001 EEWLARPLPE GLQAFGAVLV DAHRRITDPE RDIQDFVLTA ELSRHPRAYT
1051 NKRLAHLTVY YKLMARRAQV PSIKDRIPYV IVAQTREVEE TVARLAALRE
1101 LDAAAPGDEP APPAALPSA KRPRETPSHA DPPGGASKPR KLLVSELAED
50 1151 PGYAIARGVP LNTDYYFSLH LGAACVTFKA LFGNNAKITE SLLKRFPET
1201 WHPPDDVAAR LRAAGFGPAG AGATAEETRR MLHRAFDTLA *

SEQ.ID.NO. 5 DNA sequence of DNA polymerase gene for HSV1-KOS-M1

1 ATGTTTTCCG GTGGCGGCGG CCCGCTGTCC CCCGGAGGAA AGTCGGCGGC
5 51 CAGGGCGGCG TCCGGGTTTT TTGCGCCCGC CGGCCCTCGC GGAGCCGGCC
101 GGGGACCCCC GCCTTGTTTG AGGCAAACT TTTACAACCC CTACCTCGCC
151 CCAGTCGGGA CGCAACAGAA GCCGACCGGG CCAACCCAGC GCCATACGTA
10 201 CTATAGCGAA TGCATGAAT TTCGATTCAT CGCCCCGCGG GTGCTGGACG
251 AGGATGCCCC CCCGGAGAAG CGCGCCGGGG TGCACGACGG TCACCTCAAG
15 301 CGCGCCCCCA AGGTGTACTG CGGGGGGGAC GAGCGCGACG TCCTCCGCGT
351 CGGGTCGGGC GGCTTCTGGC CGCGGCGCTC GCGCCTGTGG GGCGGCGTGG
401 ACCACGCCCC GGCGGGGTTC AACCACACCG TCACCGTCTT TCACGTGTAC
20 451 GACATCCTGG AGAACGTGGA GCACGCGTAC GGCATGCGCG CGGCCCAATT
501 CCACGCGCGG TTTATGGACG CCATCACACC GACGGGGACC GTCATCACGC
25 551 TCCTGGGCCT GACTCCGGA GGCCACCGGG TGGCCGTTCA CGTTTACGGC
601 ACGCGGCAGT ACTTTTACAT GAACAAGGAG GAGGTTGACA GGCACCTACA
651 ATGCCGCGCC CCACGAGATC TCTGCGAGCG CATGGCCGCG GCCCTGCGCG
30 701 AGTCCCCGGG CGCGTCGTTC CGCGGCATCT CCGCGGACCA CTTCGAGGCG
751 GAGGTGGTGG AGCGCACCGA CGTGTACTAC TACGAGACGC GCCCCGCTCT
35 801 GTTTTACCGC GTCTACGTCC GAAGCGGGCG CGTGCTGTCT TACCTGTGCG
851 ACAACTTCTG CCCGGCCATC AAGAAGTACG AGGGTGGGGT CGACGCCACC
901 ACCCGGTTCA TCCTGGACAA CCCCAGGTTC GTCACCTTCG GCTGGTACCG
40 951 TCTCAAACCG GGCCGGAACA ACACGCTAGC CCAGCCGCGG GCCCCGATGG
1001 CCTTCGGGAC ATCCAGCGAC GTCGAGTTTA ACTGTACGGC GGACAACCTG
45 1051 GCCATCGAGG GGGGCATGAG CGACCTACCG GCATACAAGC TCATGTGCTT
1101 CGATATCGAA TGCAAGGCGG GGGGGGAGGA CGAGCTGGCC TTTCCGGTGG
1151 CCGGGCACCC GGAGGACCTG GTTATTCAGA TATCCTGTCT GCTCTACGAC
50 1201 CTGTCCACCA CCGCCCTGGA GCACGTCCTC CTGTTTTTCG TCGGTTCTCTG
1251 CGACCTCCCC GAATCCCACC TGAACGAGCT GGCGGCCAGG GGCCTGCCCA
55 1301 CGCCCGTGGT TCTGGAATTC GACAGCGAAT TCGAGATGCT GTTGGCCTTC
1351 ATGACCCTTG TGAAACAGTA CGGCCCCGAG TTCGTGACCG GGTACAACAT
1401 CATCAACTTC GACTGGCCCT TCTTGCTGGC CAAGTTGACG GACATTTACA
60

1451 AGGTCCCCCT GGACGGGTAC GGCCGCATGA ACGGCCGGGG CGTGTTTCGC
1501 GTGTGGGACA TAGGCCAGAG CCACTTCCAG AAGCGCAGCA AGATAAAGGT
5 1551 GAACGGCATG GTGAACATCG ACATGTACGG GATCATAACC GACAAGATCA
1601 AGCTCTCGAG CTACAAGCTC AACGCCGTGG CCGAAGCCGT CCTGAAGGAC
1651 AAGAAGAAGG ACCTGAGCTA TCGCGACATC CCCGCCTACT ACGCCGCCGG
10 1701 GCCCGCGCAA CGCGGGGTGA TCGGCGAGTA CTGCATACAG GATTCCCTGC
1751 TGGTGGGCCA GCTGTTTTTT AAGTTTTTGC CCCATCTGGA GCTCTCGGCC
1801 GTCGCGCGCT TGGCGGGTAT TAACATCACC CGCACCATCT ACGACGGCCA
1851 GCAGATCCGC GTCTTTACGT GCCTGCTGCG CCTGGCCGAC CAGAAGGGCT
1901 TTATTCTGCC GGACACCCAG GGGCGATTTA GGGGCGCCGG GGGGGAGGCG
20 1951 CCCAAGCGTC CGGCCGAGC CCGGGAGGAC GAGGAGCGGC CAGAGGAGGA
2001 GGGGGAGGAC GAGGACGAAC GCGAGGAGGG CGGGGGCGAG CGGGAGCCGG
25 2051 AGGGCGCGCG GGAGACCGCC GGCCGGCACG TGGGGTACCA GGGGGCCAGG
2101 GTCCTTGACC CCACTTCCGG GTTTCACGTG AACCCCGTGG TGGTGTTCTGA
2151 CTTTGCCAGC CTGTACCCCA GCATCATCCA GGCCACAAC CTGTGCTTCA
30 2201 GCACGCTCTC CCTGAGGGCC GACGCAGTGG CGCACCTGGA GCGGGGCAAG
2251 GACTACCTGG AGATCGAGGT GGGGGGGCGA CGGCTGTTCT TCGTCAAGGC
2301 TCACGTGCGA GAGAGCCTCC TCAGCATCCT CCTGCGGGAC TGGCTCGCCA
35 2351 TGCGAAAGCA GATCCGCTCG CGGATTCCCC AGAGCAGCCC CGAGGAGGCC
2401 GTGCTCCTGG ACAAGCAGCA GGCCGCCATC AAGGTCGTGT GTAACCTCGGT
40 2451 GTACGGGTTC ACGGGAGCGC AGCACGGA CTGCGCGTGC CTGCACGTTG
2501 CCGCGACGGT GACGACCATC GGCCGCGAGA TGCTGCTCGC GACCCGCGAG
2551 TACGTCCACG CGCGCTGGGC GGCCTTCGAA CAGCTCCTGG CCGATTTCCT
45 2601 GGAGGCGGCC GACATGCGCG CCCCCGGGCC CTATTCCATG CGCATCATCT
2651 ACGGGGACAC GGA CTCCATA TTTGTGCTGT GCCGCGGCCT CACGGCCGCC
50 2701 GGGCTGACGG CCATGGGCGA CAAGATGGCG AGCCACATCT CGCGCGCGCT
2751 GTTTCTGCCC CCCATCAAAC TCGAGTGCGA AAAGACGTTC ACCAAGCTGC
2801 TGCTGATCGC CAAGAAAAAG TACATCGGCG TCATCTACGG GGGTAAGATG
55 2851 CTCATCAAGG GCGTGGATCT GGTGCGCAA AACA ACTGCG CGTTTATCAA
2901 CCGCACCTCC AGGGCCCTGG TCGACCTGCT GTTTTACGAC GATACCGTAT
60

2951 CCGGAGCGGC CGCCGCGTTA GCCGAGCGCC CCGCAGAGGA GTGGCTGGCG
3001 CGACCCCTGC CCGAGGGACT GCAGGCGTTC GGGGCCGTCC TCGTAGACGC
5 3051 CCATCGGCGC ATCACCGACC CGGAGAGGGA CATCCAGGAC TTTGTCCTCA
3101 CCGCCGA ACT GAGCAGACAC CCGCGCGCGT ACACCAACAA GCGCCTGGCC
3151 CACCTGACGG TGTATTACAA GTCATGGCC CGCCGCGCGC AGGTCCCCGTC
10 3201 CATCAAGGAC CGGATCCCGT ACGTGATCGT GGCCAGACC CGCGAGGTAG
3251 AGGAGACGGT CGCGCGGCTG GCCGCCCTCC GCGAGCTAGA CGCCGCCGCC
15 3301 CCAGGGGACG AGCCCGCCCC CCGCGCGGCC CTGCCCTCCC CGGCCAAGCG
3351 CCCCCGGGAG ACGCCGTCGC ATGCCGACCC CCGGGAGGC GCGTCCAAGC
3401 CCCGCAAGCT GCTGGTGTCC GAGCTGGCCG AGGATCCCGC ATACGCCATT
20 3451 GCCCACGGCG TCGCCCTGAA CACGGACTAT TACTTCTCCC ACCTGTTGGG
3501 GGCGGCGTGC GTGACATTCA AGGCCCTGTT TGGGAATAAC GCCAAGATCA
25 3551 CCGAGAGTCT GTTAAAAAGG TTTATTCCCG AAGTGTGGCA CCCCCGGAC
3601 GACGTGGCCG CGCGGCTCCG GGCCGCAGGG TTCGGGGCGG TGGGTGCCGG
3651 CGCTACGGCG GAGGAACTC GTCGAATGTT GCATAGAGCC TTTGATACTC
30 3701 TAGCATGA

SEQ.ID.NO. 6 Amino acid sequence of DNA polymerase for HSV1-KOS-M1

1 MFSGGGGPLS PGGKSAARAA SGFFAPAGPR GAGRGPPPCL RQNFYNPYLA
5 51 PVGTQQKPTG PTQRHTYYSE CDEFRFIAPR VLDEDAPPEK RAGVHDGHLK
101 RAPKVYCGGD ERDVLRVGSG GFWPRRSRLW GGVDHAPAGF NPTVTVFHVY
10 151 DILENVEHAY GMRAAQFHAR FMDAITPTGT VITLLGLTPE GHRVAVHVYG
201 TRQYFYMNKE EVDRHLQCRA PRDLCERMAA ALRESPGASF RGISADHFEA
251 EVVERTDVYY YETRPALFYR VYVRSGRVLS YLCDNFCPAI KKYEGGVDAT
15 301 TRFILDNPGF VTFGWYRLKP GRNNTLAQPR APMAFGTSSD VEFNCTADNL
351 AIEGGMSDLP AYKLMCFDIE CKAGGEDELA FPVAGHPEDL VIQISCLLYD
20 401 LSTTALEHVL LFSLGSCDLP ESHLNELAAR GLPTPVVLEF DSEFEMLLAF
451 MTLVKQYGPE FVTGYNIINF DWPFLAKLT DIYKVPLDGY GRMNGRGVFR
501 VWDIGQSHFQ KRSKIKVNGM VNIDMYGIIT DKIKLSSYKL NAVA EAVLKD
25 551 KKKDLSYRDI PAYYAAGPAQ RGVIGEYCIQ DSLLVGQLFF KFLPHLELSA
601 VARLAGINIT RTTYDGQQIR VFTCLRLAD QKGFIPLDTQ GRFRGAGGEA
30 651 PKRPAAARED EERPEEEGED EDEREEGGGE REPEGARETA GRHVGYYQAR
701 VLDPTSGFHV NPVVVDFDAS LYPSIIQAHN LCFSTLSLRA DAVAHLEAGK
751 DYLEIEVGGR RLFFVKAHVR ESLLSILLRD WLAMRKQIRS RIPQSSPEEA
35 801 VLLDKQQA AI KVV CNSVYGF TGAQHGLLPC LHVAATVT TI GREMLLATRE
851 YVHARWAAFE QLLADFPEAA DMRAPGPYSM RIYGD TDSI FVLCRGLTAA
40 901 GLTAMGDKMA SHISRALFLP PIKLECEKTF TKLLLIAKKK YIGVIYGGKM
951 LIKGVDLVRK NNCAFINRTS RALVDLLFYD DTVSGAAAAL AERPABEWLA
1001 RPLPEGLQAF GAVLVDAHRR ITDPERDIQD FVLTAELSRH PRAYTNKRLA
45 1051 HLTVYYKLMA RRAQVPSIKD RPYVIVAQT REVEETVARL AALRELDAAA
1101 PGDEPAPPAA LPSPAKRPRE TPSHADPPGG ASKPRKLLVS ELAEDPAYAI
50 1151 AHGVALNTDY YFSHLLGAAC VTFKALFGNN AKITESLLKR FIPEVWHPPD
1201 DVAARLRAAG FGAVGAGATA EETRMLHRA FDTLA*

SEQ.ID.NO. 7 DNA sequence of HSV polymerase gene for HSV1-F-M1

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1  ATGTTTTCCG GTGGCGGCGG CCCGCTGTCC CCCGGAGGAA AGTCGGCGGC
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51  CAGGGCGGCG TCCGGGTTTT TTGCGCCCGC CGGCCCTCGC GGAGCCGGCC
101 GGGGACCCCC GCCTTGCTTG AGGCAAACT TTTACAACCC CTACCTCGCC
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151 CCAGTCGGGA CGCAACAGAA GCCGACCGGG CCAACCCAGC GCCATACGTA
201 CTATAGCGAA TCGATGAAT TTCGATTCAT CGCCCCGCGG GTGCTGGACG
251 AGGATGCCCC CCCGAGAAAG CGCGCCGGGG TGCACGACGG TCACCTCAAG
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301 CGCGCCCCCA AGGTGTACTG CGGGGGGGAC GAGCGCGACG TCCTCCGCGT
351 CGGGTCGGGC GGCTTCTGGC CGCGGCGCTC GCGCCTGTGG GCGGCGGTGG
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401 ACCACGCCCC GCGGGGGTTC AACCCACCG TCACCGTCTT TCACGTGTAC
451 GACATCCTGG AGAACGTGGA GCACGCGTAC GGCATGCGCG CGGCCCAGTT
501 CCACGCGCGG TTTATGGACG CCATCACACC GACGGGGACC GTCATCACGC
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551 TCCTGGGCCT GACTCCGGA GGCACCGGG TGGCCGTTC CGTTTACGGC
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651 ATGCCGCGCC CCACGAGATC TCTGCGAGCG CATGGCCGCG GCCCTGCGCG
701 AGTCCCCGGG CGCGTCGTTC CGCGGCATTT CCGCGGACCA CTTTCGAGCG
751 GAGGTGGTGG AGCGCACCAG CGTGTACTAC TACGAGACGC GCCCCGCTCT
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801 GTTTTACCGC GTCTACGTCC GAAGCGGGCG CGTGCTGTCT TACCTGTGCG
851 ACAACTTCTG CCCGGCCATC AAGAAGTACG AGGGTGGGGT CGACGCCACC
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901 ACCCGGTTCA TCCTGGACAA CCCC GG GTTC GTACCTTCG GCTGGTACCG
951 TCTCAAACCG GGCCGGAACA ACACGCTAGC CCAGCCGCGG GCCCCGATGG
1001 CCTTCGGGAC ATCCAGCGAC GTCGAGTTTA ACTGTACGGC GGACAACCTG
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1251 CGACCTCCCC GAATCCCACC TGAACGAGCT GCGCGCCAGG GGCCTGCCCCA
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1451 AGGTCCCCCT GGACGGGTAC GGCCGCATGA ACGGCCGGGG CGTGTTTCGC
1501 GTGTGGGACA TAGGCCAGAG CCACTTCCAG AAGCGCAGCA AGATAAAGGT
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1551 GAACGGCATG GTGAACATCG ACATGTACGG GATTATAACC GACAAGATCA

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5 1701 GCCCGCGCAA CGCGGGGTGA TCGGCGAGTA CTGCATACAG GATTCCCTGC
1751 TGGTGGGCCA GCTGTTTTTT AAGTTTTTGC CCCATCTGGA GCTCTCGGCC
10 1801 GTCGCGCGCT TGGCGGGTAT TAACATCACC CGCACCATCT ACGACGGCCA
1851 GCAGATCCGC GTCTTTACGT GCCTGCTGCG CCTGGCCGAC CAGAAGGGCT
1901 TTATTCTGCC GGACACCCAG GGGCGATTTA GGGGCGGCGG GGGGGAGGCG
15 1951 CCCAAGCGTC CGGCCGCAGC CCGGGAGGAC GAGGAGCGGC CAGAGGAGGA
2001 GGGGGAGGAC GAGGACGAAC GCGAGGAGGG CGGGGCGGAG CGGGAGCCGG
20 2051 AGGGCGCGCG GGAGACCGCC GGCCGGCAGG TGGGGTACCA GGGGGCCAGG
2101 GTCCTTGACC CCACTTCCGG GTTTCATGTG AACCCCGTGG TGGTGTTCGA
2151 CTTTGCCAGC CTGTACCCCA GCATCATCCA GGCCACAAC CTGTGCTTCA
25 2201 GCACGCTCTC CCTGAGGGCC GACGCAGTGG CGCACCTGGA GGCGGGCAAG
2251 GACTACCTGG AGATCGAGGT GGGGGGGCGA CGGCTGTTCT TCGTCAAGGC
30 2301 TCACGTGCGA GAGAGCCTCC TCAGCATCCT CCGCGGGGAC TGGCTCGCCA
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2401 GTGCTCCTGG ACAAGCAGCA GGCCGCCATC AAGGTCGTGT GTAACCTCGGT
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40 2551 TACGTCCACG CGCGCTGGGC GGCCCTCGAA CAGCTCCTGG CCGATTTCCT
2601 GGAGGCGGCC GACATGCGCG CCCCCGGGCC CTATTCCATG CGCATCATCT
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45 2701 GGGCTGACGG CCGTGGGCGA CAAGATGGCG AGCCACATCT CGCGCGCGCT
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50 2801 TGCTGATCGC CAAGAAAAAG TACATCGGCG TCATCTACGG GGGTAAGATG
2851 CTCATCAAGG GCGTGGATCT GGTGCGCAA AACAACTGCG CGTTTATCAA
2901 CCGCACCTCC AGGGCCCTGG TCGACCTGCT GTTTTACGAC GATACCGTAT
55 2951 CCGGAGCGGC CGCCGCGTTA GCCGAGCGCC CCGCAGAGGA GTGGCTGGCG
3001 CGACCCCTGC CCGAGGGACT GCAGGCGTTC GGGGCCGTCC TCGTAGACGC
60 3051 CCATCGGCGC ATCACCAGAC CGGAGAGGGA CATCCAGGAC TTTGTCCTCA
3101 CCGCCGAAGT GAGCAGACAC CCGCGCGCGT ACACCAACAA GCGCCTGGCC
3151 CACCTGACGG TGTATTACAA GTCATGGCC CGCCGCGCGC AGGTCCCGTC
65 3201 CATCAAGGAC CGGATCCCGT ACGTGATCGT GGCCAGACC CGCGAGGTAG

3251 AGGAGACGGT CGCGCGGCTG GCCGCCCTCC GCGAGCTCGA CGCCGCCGCC
3301 CCAGGGGACG AGCCCGCCCC CCGCGCGGCC CTGCCCTCCC CGGCCAAGCG
5 3351 CCCCCGGGAG ACGCCGTTGC ATGCCGACCC CCCGGGAGGC GCGTCCAAGC
3401 CCCGCAAGCT GCTGGTGTCC GAGCTGGCCG AGGATCCCGC ATACGCCATT
3451 GCCCACGGCG TCGCCCTGAA CACGGACTAT TACTTCTCCC ACCTGTTGGG
10 3501 GCGGCGGTGC GTGACATTCA AGGCCCTGTT TGGGAATAAC GCCAAGATCA
3551 CCGAGAGTCT GTTAAAAAGG TTTATTCCCG AAGTGTGGCA CCCCCCGGAC
15 3601 GACGTGGCCG CGCGGCTCCG GGCCGCAGGG TTCGGGGCGG TGGGTGCCGG
3651 CGCTACGGCG GAGGAAACTC GTCGAATGTT GCATAGAGCC TTTGATACTC
3701 TAGCATGA

SEQ.ID.NO. 8 Amino acid sequence of DNA polymerase for HSV1-F-M1

1 MFSGGGGPLS PGGKSAARAA SGFFAPAGPR GAGRGPPLCL RQNFYNPYLA
5 51 PVGTQQKPTG PTQRHTYYSE CDEFRIAPR VLDEDAPPEK RAGVHDGHLK
101 RAPKVYCGGD ERDVLRVGSG GFWPRRSRLW GGVDHAPAGF NPTVTVFHVY
151 DILENVEHAY GMRAAQFHAR FMDAITPTGT VITLLGLTPE GHRVAVHVY
10 201 TRQYFYMNKE EVDRHLQCRA PRDLCERMAA ALRESPGASF RGISADHFEA
251 EVVERTDVYY YETRPALFYR VYVRSRVLV YLCDNFCAI KKYEGGVDAT
15 301 TRFILDNPGF VTFGWYRLKP GRNNTLAQPR APMAFGTSSD VEFNCTADNL
351 AIEGGMSDLP AYKLMCFDIE CKAGGEDELA FPVAGHPEDL VIQISCLLYD
401 LSTTALEHVL LFSLGSCDLP ESHLNELAAR GLPTPVVLEF DSEFEMLLAF
20 451 MTLVKQYGPE FVTGYNIINF DWPFLAKLT DIYKVPLDGY GRMNRGVFR
501 VWDIGQSHFQ KRSKIKVNGM VNIDMYGIIT DKIKLSSYKL NAVAEAVLKD
25 551 KKKDLSYRDI PAYYAAGPAQ RGVIGEYCIQ DSLLVGQLFF KFLPHLELSA
601 VARLAGINIT RTTYDGQQR VFTCLRLAD QKGFLPDTQ GRFRGGGGEA
651 PKRPAAAREE EERPEEEGED EDEREEGGGE REPEGARETA GRHVGYYQAR
30 701 VLDPTSGFHV NPVVVFDFAS LYPSTIAHN LCFSTLSLRA DAVAHLEAGK
751 DYLEIEVGGR RLFFVKAHVR ESLLSILLRD WLAMRKQIRS RIPQSSPEEA
35 801 VLLDKQQAII KVVCSVYGF TGAQHGLLPC LHVAATVTTI GREMLLATRE
851 YVHARWAAFE QLLADFPEAA DMRAPGPYSM RIYGDTSI FVLCRGLTAA
901 GLTAVGDKMA SHISRALFLS PIKLECEKTF TKLLLIAKKK YIGVIYGGKM
40 951 LIKGVDLVRK NNCAFINRTS RALVDLLFYD DTVSGAAAAL AERPAAEWLA
1001 RPLPEGLQAF GAVLVDAHRR ITDPERDIQD FVLTAELSRH PRAYTNKRLA
45 1051 HLTVYYKLMA RRAQVPSIKD RPYVIVAQT REVEETVARL AALRELDAAA
1101 PGDEPAPPAA LPSPAKRPRE TPLHADPPGG ASKPRKLLVS ELAEDPAYAI
1151 AHGVALNTDY YFSHLLGAAC VTFKALFGNN AKITESLLKR FIPEVWHPPD
50 1201 DVAARLRAAG FGAVGAGATA EETRRMLHRA FDTLA*

SEQ.ID.NO. 9 DNA sequence of HSV polymerase gene for HSV1-DJL-M1

1 ATGTTTCCG GTGGCGGCGG CCCGCTGTCC CCCGGAGGAA AGTCGGCGGC
5 51 CAGGGCGGCG TCCGGGTTTT TTGCGCCCGC CGGCCCTCGC GGAGCCGGCC
101 GGGGACCCCC GCCTTGTTTG AGGCAAACT TTTACAACCC CTACCTCGCC
151 CCAGTCGGGA CGCAACAGAA GCCGACCGGG CCAACCCAGC GCCATACGTA
10 201 CTATAGCGAA TGCATGAAT TTCGATTCAT CGCCCCGCGG GTGCTGGACG
251 AGGATGCCCC CCCGGAGAAG CGCGCCGGGG TGCACGACGG TCACCTCAAG
15 301 CGCGCCCCCA AGGTGTACTG CGGGGGGGAC GAGCGCGACG TCCTCCGCGT
351 CGGGTCGGGC GGCTTCTGGC CGCGGCGCTC GCGCCTGTGG GGCGGCGTGG
401 ACCACGCCCC GCGGGGGTTC AACCCACCG TCACCGTCTT TCACGTGTAT
20 451 GACATCCTGG AGAACGTGGA GCACGCGTAC GGCATGCGCG CGGCCAGTT
501 CCACGCGCGG TTTATGGACG CCATCACACC GACGGGGACC GTCATCACGC
25 551 TCCTGGGCCT GACTCCGGAA GGCCACCGGG TGGCCGTTCA CGTTTACGGC
601 ACGCGGCAGT ACTTTTACAT GAACAAGGAG GAGGTTGACA GGCACCTACA
651 ATGCCGCGCC CCACGAGATC TCTGCGAGCG CATGGCCGCG GCCCTGCGCG
30 701 AGTCCCCGGG CGCGTCGTTT CGCGGCATCT CCGCGGACCA CTTCGAGGCG
751 GAGGTGGTGG AGCGC'ACCGA CGTGTACTAC TACGAGACGC GCCCCGCTCT
35 801 GTTTTACCGC GTCTACGTCC GAAGCGGGCG CGTGCTGTCT TACCTGTGCG
851 ACAACTTCTG CCCGGCCATC AAGAAGTACG AGGGTGGGGT CGACGCCACC
901 ACCCGGTTCA TCCTGGACAA CCCCAGGTTC GTCACCTTCG GCTGGTACCG
40 951 TCTCAAACCG GGCCGGAACA ACACGCTAGC CCAGCCGCGG GCCCCGATGG
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55 1301 CGCCCGTGGT TCTGGAATTC GACAGCGAAT TCGAGATGCT GTTGGCCTTC
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25 2051 AGGGCGCGCG GGAGACCGCC GGCCGGCACG TGGGGTACCA GGGGGCCAGG
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30 2151 CTTTGCCAGC CTGTACCCCA GCATCATCCA GGCCACAAC CTGTGCTTCA
2201 GCACGCTCTC CCTGAGGGCC GACGCAGTGG CGCACCTGGA GCGGGGCAAG
2251 GACTACCTGG AGATCGAGGT GGGGGGGCGA CGGCTGTTCT TCGTCAAGGC
35 2301 TCACGTGCGA GAGAGCCTCC TCAGCATCCT CCTGCGGGAC TGGCTCGCCA
2351 TGCGAAAGCA GATCCGCTCG CGGATTCCCC AGAGCAGCCC CGAGGAGGCC
40 2401 GTGCTCCTGG ACAAGCAGCA GGCCGCCATC AAGGTCGTGT GTAACTCGGT
2451 TTACGGGTTC ACGGGAGCGC AGCACGGA CTGCGCTGC CTGCACGTTG
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45 2551 TACGTCCACG CGCGCTGGGC GGCCTTCGAA CAGCTCCTGG CCGATTTCCT
2601 GGAGGCGGCC GACATGCGCG CCCCCGGGCC CTATTCCATG CGCATCATCT
50 2651 ACGGGGACAC GGA CTCCATA TTTGTGCTGT GCCGCGGCCT CACGGCCGCC
2701 GGGCTGACGG CCGTGGGCGA CAAGATGGCG AGCCACATCT CGCGCGCGCT
2751 GTTCTGCCC CCCATCAAAC TCGAGTGCGA AAAGACGTT ACCAAGCTGC
55 2801 TGCTGATCGC CAAGAAAAAG TACATCGGCG TCATCTACGG GGGTAAGATG
2851 CTCATCAAGG GCGTGGATCT GGTGCGCAA AACAACTGCG CGTTTATCAA
60 2901 CCGCACCTCC AGGGCCCTGG TCGACCTGCT GTTTTACGAC GATACCGTAT

2951 CCGGAGCGGC CGCCGCGTTA GCCGAGCGCC CCGCAGAGGA GTGGCTGGCG
3001 CGACCCCTGC CCGAGGGACT GCAGGCGTTC GGGGCCGTCC TCGTAGACGC
5 3051 CCATCGGCGC ATCACCGACC CGGAGAGGGA CATCCAGGAC TTTGTTCTCA
3101 CCGCCGAACT GAGCAGACAC CCGCGCGCGT ACACCAACAA GCGCCTGGCC
10 3151 CACCTGACGG TGTATTACAA GTCATGGCC CGCCGCGCGC AGGTCCCCTC
3201 CATCAAGGAC CGGATCCCGT ACGTGATCGT GGCCAGACC CGCGAGGTAG
3251 AGGAGACGGT CGCGCGGCTG GCCGCCCTCC GCGAGCTAGA CGCCGCCGCC
15 3301 CCAGGGGACG AGCCCGCCCC CCGCGGCC CTGCCCTCCC CGGCCAAGCG
3351 CCCCCGGGAG ACGCCGTCGC CTGCCGACCC CCGGGAGGC GCGTCCAAGC
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3451 GCCCACGGCG TCGCCCTGAA CACGGAATAT TACTTCTCCC ACCTGTTGGG
3501 GGCGGCGTGC GTGACATTCA AGGCCCTGTT TGGGAATAAC GCCAAGATCA
25 3551 CCGAGAGTCT GTTAAAAAGG TTTATTCCCG AAGTGTGGCA CCCCCGGAC
3601 GACGTGGCCG CGCGGCTCCG GACCGCAGGG TTCGGGGCGG TGGGTGCCGG
30 3651 CGCTACGGCG GAGGAACTC GTCGAATGTT GCATAGAGCC TTTGATACTC
3701 TAGCATGA

SEQ.ID.NO. 10 Amino acid sequence of DNA polymerase for HSV1-DJL-M1

1 MFSGGGGPLS PGGKSAARAA SGFFAPAGPR GAGRGPPLCL RQNFYNPYLA
5 51 PVGTQKPTG PTQRHTYYSE CDEFRIAPR VLDEDAPEK RAGVHDGHLK
101 RAPKVYCGGD ERDVLRVGSG GFWPRRSRLW GGVDHAPAGF NPTVTVFHVY
151 DILENVEHAY GMRAAQFHAR FMDAITPTGT VITLLGLTPE GHRVAVHVY
10 201 TRQYFYMNKE EVDRHLQCRA PRDLCERMAA ALRESPGASF RGISADHFEA
251 EVVERTDVYY YETRPALFYR VYVRSRVLV YLCDNFCAI KKYEGGVDAT
15 301 TRFILDNPGF VTFGWYRLKP GRNNTLAQPR APMAFGTSSD VEFNCTADNL
351 AIEGGMSDLP AYKLMCFDIE CKAGGEDELA FPVAGHPEDL VIQISCLLYD
401 LSTTALEHVL LFSLGSCDLP ESHLNELAAR GLTPVVLEF DSEFEMLLAF
20 451 MTLVKQYGPE FVTGYNINP DWPFLAKLT DIYKVPLDGY GRMNGRGVFR
501 VWDIGQSHFQ KRSKIKVNGM VNIDMYGIT DKIKLSSYKL NAVAEAVLKD
25 551 KKKDLSYRDI PTYYAAGPAQ RGVIGEYCIQ DSVLVGQLFF KFLPHLELSA
601 VARLAGINIT RTIYDGQQIR VFTCLRLAD QKGFILPDTQ GRFRGAGGEA
651 PKRPAAAREE EERPEEEGED ENEREEGGGE REPEGARETA GRHVG YQGAR
30 701 VLDPTSGFHV NPVVVDFAS LYPSTIAHN LCFSTLSLRA DAVAHLEAGK
751 DYLEIEVGGR RLFFVKAHVR ESLLSILLRD WLAMRKQIRS RIPQSSPEEA
35 801 VLLDKQAAI KVV CNSVYGF TGAQHGLLPC LHVAATVTTI GREMLLATRE
851 YVHARWAAFE QLLADFPEAA DMRAPGPYSM RIYGD TDSI FVLCRGLTAA
901 GLTAVGDKMA SHISRALFLP PIKLECEKTF TKLLLIAKKK YIGVIYGGKM
40 951 LIKGVDLVRK NNCAFINRTS RALVDLLFYD DTVSGAAAAL AERPAAEWLA
1001 RPLPEGLQAF GAVLVDAHRR ITDPERDIQD FVLTAELSRH PRAYTNKRLA
45 1051 HLTVYYKLMA RRAQVPSIKD RPYVIVAQT REVEETVARL AALRELDAAA
1101 PGDEPAPPAA LPSPAKRPRE TPSPADPPGG ASKPRKLLVS ELAEDPAYAI
1151 AHGVALNTDY YFSHLLGAAC VTFKALFGNN AKITESLLKR FIPEVWHPPD
50 1201 DVAARLRTAG FGAVGAGATA EETRMLHRA FDTLA*

SEQ.ID.NO. 11 DNA sequence of DNA polymerase gene for HMCV-AD169-M1

1 ATGTTTTTCA ACCCGTATCT GAGCGGCGGC GTGACCGGCG GTGCGGTTCG
5 51 GGGTGGCCGG CGTCAGCGTT CGCAGCCCGG CTCCGCGCAG GGCTCGGGCA
101 AGCGGCCGCC ACAGAAACAG TTTTTCAGA TCGTGCCGCG AGGTGTCATG
151 TTCGACGGTC AGACGGGGTT GATCAAGCAT AAGACGGGAC GGCTGCCTCT
10 201 CATGTTCTAT CGAGAGATTA AACATTTGTT GAGTCATGAC ATGGTTTGGC
251 CGTGTCTTG GCGCGAGACC CTGGTGGGTC GCGTGGTGGG ACCTATTCGT
301 TTTCACACCT ACGATCAGAC GGACGCCGTG CTCTTCTTCG ACTCGCCCGA
351 AAACGTGTCG CCGCGCTATC GTCAGCATCT GGTGCCTTCG GGGAACGTGT
401 TGCCTTTCTT CGGGGCCACA GAACACGGCT ACAGTATCTG CGTCAACGTT
20 451 TTCGGGCAGC GCAGCTACTT TTAAGTGAG TACAGCGACA CCGATAGGCT
501 GCGTGAGGTC ATTGCCAGCG TGGGCGAACT AGTGCCCGAA CCGCGGACGC
25 551 CATA CGCCGT GTCTGTCACG CCGGCCACCA AGACCTCCAT CTATGGGTAC
601 GGGACGCGAC CCGTGCCCGA TTGTCAGTGT GTGTCTATCA GCAACTGGAC
651 CATGGCCAGA AAAATCGGCG AGTATCTGCT GGAGCAGGGT TTTCCCGTGT
30 701 ACGAGGTCCG TGTGGATCCG CTGACGCGTT TGGTCATCGA TCGGCGGATC
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35 801 TCGCGGTCG ACTTGTGATA TCGAGGTAGA CTGCGATGTC TCTGACCTGG
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55 1301 AGTTGCCTAC GGCGCAGGGC GGCCGTTTCT TTTTACACAG CCCC GCCGTG
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5 1551 TTACAAGGAC ATCCCGCGTT GTTTCGTGGC TAATGCCGAG GGCCGCGCCC
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10 1651 AACACCATTA ATTTTCACTA CGAGGCCGGG GCCATCGCGC GGCTGGCTAA
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15 1801 TACAGCAAAG GTACGACGGT GCCCGAAACG AATAGCGTTG CTGTGTCACC
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2001 CGTTTTTCAGC GTCGGCTCCG GCAGTAGTGG CGGCGTCGGC GTTTCCAACG
25 2051 ACAATCACGG CGCCGGCGGT ACTGCGGCGG TTTCGTACCA GGGCGCCACG
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SEQ. ID. NO. 12 Amino acid sequence of DNA polymerase for HCMV-AD169-M1

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50 1151 GEPAKKRARK PPSAVCNYEV AEDPSYVREH GVPIHADKYF EQVLKAVTNV
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Figure 6**SEQ.ID.NO.13****Amino acid sequence of DNA polymerase for HCMV-AD169**

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SEQUENCE LISTING

<110> Homa, Fred
 Wathen, Michael
 Hopkins, Todd
 Thomsen, Darrell

<120> A Method for Treating Herpes Virus

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 <211> 1240
 <212> PRT
 <213> herpes simplex

<400> 4

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 35 40 45
 His Leu Ala Gln Thr Gly Thr Gln Pro Lys Ala Pro Gly Pro Ala Gln
 50 55 60
 Arg His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro
 65 70 75 80
 Arg Ser Leu Asp Glu Asp Ala Pro Ala Glu Gln Arg Thr Gly Val His
 85 90 95
 Asp Gly Arg Leu Arg Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu
 100 105 110
 Arg Asp Val Leu Arg Val Gly Pro Glu Gly Phe Trp Pro Arg Arg Leu
 115 120 125
 Arg Leu Trp Gly Gly Ala Asp His Ala Pro Glu Gly Phe Asp Pro Thr
 130 135 140
 Val Thr Val Phe His Val Tyr Asp Ile Leu Glu His Val Glu His Ala

145		150		155		160
Tyr Ser Met Arg	Ala Ala Gln Leu His	Glu Arg Phe Met Asp	Ala Ile			
	165	170	175			
Thr Pro Ala Gly	Thr Val Ile Thr	Leu Leu Gly Leu Thr	Pro Glu Gly			
	180	185	190			
His Arg Val Ala	Val His Val Tyr	Gly Thr Arg Gln Tyr	Phe Tyr Met			
	195	200	205			
Asn Lys Ala Glu	Val Asp Arg His	Leu Gln Cys Arg	Ala Pro Arg Asp			
	210	215	220			
Leu Cys Glu Arg	Leu Ala Ala Ala	Leu Arg Glu Ser	Pro Gly Ala Ser			
	225	230	235			240
Phe Arg Gly Ile	Ser Ala Asp His	Phe Glu Ala Glu	Val Val Glu Arg			
	245	250	255			
Ala Asp Val Tyr	Tyr Tyr Glu Thr	Arg Pro Thr Leu	Tyr Tyr Arg Val			
	260	265	270			
Phe Val Arg Ser	Gly Arg Ala Leu	Ala Tyr Leu Cys	Asp Asn Phe Cys			
	275	280	285			
Pro Ala Ile Arg	Lys Tyr Glu Gly	Gly Val Asp Ala	Thr Thr Arg Phe			
	290	295	300			
Ile Leu Asp Asn	Pro Gly Phe Val	Thr Phe Gly Trp	Tyr Arg Leu Lys			
	305	310	315			320
Pro Gly Arg Gly	Asn Ala Pro Ala	Gln Pro Arg Pro	Pro Thr Ala Phe			
	325	330	335			
Gly Thr Ser Ser	Asp Val Glu Phe	Asn Cys Thr Ala	Asp Asn Leu Ala			
	340	345	350			
Val Glu Gly Ala	Met Cys Asp Leu	Pro Ala Tyr Lys	Leu Met Cys Phe			
	355	360	365			
Asp Ile Glu Cys	Lys Ala Gly Gly	Glu Asp Glu Leu	Ala Phe Pro Val			
	370	375	380			
Ala Glu Arg Pro	Glu Asp Leu Val	Ile Gln Ile Ser	Cys Leu Leu Tyr			
	385	390	395			400
Asp Leu Ser Thr	Thr Ala Leu Glu	His Ile Leu Leu	Phe Ser Leu Gly			
	405	410	415			
Ser Cys Asp Leu	Pro Glu Ser His	Leu Ser Asp Leu	Ala Ser Arg Gly			
	420	425	430			
Leu Pro Ala Pro	Val Val Leu Glu	Phe Asp Ser Glu	Phe Glu Met Leu			
	435	440	445			
Leu Ala Phe Met	Thr Phe Val Lys	Gln Tyr Gly Pro	Glu Phe Val Thr			
	450	455	460			
Gly Tyr Asn Ile	Ile Asn Phe Asp	Trp Pro Phe Val	Leu Thr Lys Leu			
	465	470	475			480

Thr Glu Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly
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 Arg Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys
 500 505 510
 Arg Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly
 515 520 525
 Ile Ile Thr Asp Lys Val Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val
 530 535 540
 Ala Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp
 545 550 555 560
 Ile Pro Ala Tyr Tyr Ala Ser Gly Pro Ala Gln Arg Gly Val Ile Gly
 565 570 575
 Glu Tyr Cys Val Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys
 580 585 590
 Phe Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile
 595 600 605
 Asn Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr
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 Cys Leu Leu Arg Leu Ala Gly Gln Lys Gly Phe Ile Leu Pro Asp Thr
 625 630 635 640
 Gln Gly Arg Phe Arg Gly Leu Asp Lys Glu Ala Pro Lys Arg Pro Ala
 645 650 655
 Val Pro Arg Gly Glu Gly Glu Arg Pro Gly Asp Gly Asn Gly Asp Glu
 660 665 670
 Asp Lys Asp Asp Asp Glu Asp Gly Asp Glu Asp Gly Asp Glu Arg Glu
 675 680 685
 Glu Val Ala Arg Glu Thr Gly Gly Arg His Val Gly Tyr Gln Gly Ala
 690 695 700
 Arg Val Leu Asp Pro Thr Ser Gly Phe His Val Asp Pro Val Val Val
 705 710 715 720
 Phe Asp Phe Ala Ser Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu
 725 730 735
 Cys Phe Ser Thr Leu Ser Leu Arg Pro Glu Ala Val Ala His Leu Glu
 740 745 750
 Ala Asp Arg Asp Tyr Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe
 755 760 765
 Phe Val Lys Ala His Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg
 770 775 780
 Asp Trp Leu Ala Met Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser
 785 790 795 800
 Pro Pro Glu Glu Ala Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys
 805 810 815

Val Val Cys Asn Ser Val Tyr Gly Phe Thr Gly Ala Gln His Gly Leu
 820 825 830
 Leu Pro Cys Leu His Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu
 835 840 845
 Met Leu Leu Ala Thr Arg Ala Tyr Val His Ala Arg Trp Ala Glu Phe
 850 855 860
 Asp Gln Leu Leu Ala Asp Phe Pro Glu Ala Ala Gly Met Arg Ala Pro
 865 870 875 880
 Gly Pro Tyr Ser Met Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe
 885 890 895
 Val Leu Cys Arg Gly Leu Thr Ala Ala Gly Leu Val Ala Met Gly Asp
 900 905 910
 Lys Met Ala Ser His Ile Ser Arg Ala Leu Phe Leu Pro Pro Ile Lys
 915 920 925
 Leu Glu Cys Glu Lys Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys
 930 935 940
 Lys Tyr Ile Gly Val Ile Cys Gly Gly Lys Met Leu Ile Lys Gly Val
 945 950 955 960
 Asp Leu Val Arg Lys Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg
 965 970 975
 Ala Leu Val Asp Leu Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala
 980 985 990
 Ala Ala Leu Ala Glu Arg Pro Ala Glu Glu Trp Leu Ala Arg Pro Leu
 995 1000 1005
 Pro Glu Gly Leu Gln Ala Phe Gly Ala Val Leu Val Asp Ala His
 1010 1015 1020
 Arg Arg Ile Thr Asp Pro Glu Arg Asp Ile Gln Asp Phe Val Leu
 1025 1030 1035
 Thr Ala Glu Leu Ser Arg His Pro Arg Ala Tyr Thr Asn Lys Arg
 1040 1045 1050
 Leu Ala His Leu Thr Val Tyr Tyr Lys Leu Met Ala Arg Arg Ala
 1055 1060 1065
 Gln Val Pro Ser Ile Lys Asp Arg Ile Pro Tyr Val Ile Val Ala
 1070 1075 1080
 Gln Thr Arg Glu Val Glu Glu Thr Val Ala Arg Leu Ala Ala Leu
 1085 1090 1095
 Arg Glu Leu Asp Ala Ala Ala Pro Gly Asp Glu Pro Ala Pro Pro
 1100 1105 1110
 Ala Ala Leu Pro Ser Pro Ala Lys Arg Pro Arg Glu Thr Pro Ser
 1115 1120 1125
 His Ala Asp Pro Pro Gly Gly Ala Ser Lys Pro Arg Lys Leu Leu

1130	1135	1140
Val Ser Glu Leu Ala Glu Asp Pro Gly Tyr Ala Ile Ala Arg Gly		
1145	1150	1155
Val Pro Leu Asn Thr Asp Tyr Tyr Phe Ser His Leu Leu Gly Ala		
1160	1165	1170
Ala Cys Val Thr Phe Lys Ala Leu Phe Gly Asn Asn Ala Lys Ile		
1175	1180	1185
Thr Glu Ser Leu Leu Lys Arg Phe Ile Pro Glu Thr Trp His Pro		
1190	1195	1200
Pro Asp Asp Val Ala Ala Arg Leu Arg Ala Ala Gly Phe Gly Pro		
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Ala Gly Ala Gly Ala Thr Ala Glu Glu Thr Arg Arg Met Leu His		
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Arg Ala Phe Asp Thr Leu Ala		
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 <211> 3708
 <212> DNA
 <213> herpes simplex

<400> 5
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<210> 6
<211> 1235
<212> PRT
<213> herpes simplex

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<400> 6

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Gly Arg Gly Pro Pro Pro Cys Leu Arg Gln Asn Phe Tyr Asn Pro Tyr
          35          40          45

Leu Ala Pro Val Gly Thr Gln Gln Lys Pro Thr Gly Pro Thr Gln Arg
          50          55          60

His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro Arg
          65          70          75          80

Val Leu Asp Glu Asp Ala Pro Pro Glu Lys Arg Ala Gly Val His Asp
          85          90          95

Gly His Leu Lys Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu Arg
          100         105         110

Asp Val Leu Arg Val Gly Ser Gly Gly Phe Trp Pro Arg Arg Ser Arg
          115         120         125

Leu Trp Gly Gly Val Asp His Ala Pro Ala Gly Phe Asn Pro Thr Val

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Pro Thr Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly His		
	180	185 190
Arg Val Ala Val His Val Tyr Gly Thr Arg Gln Tyr Phe Tyr Met Asn		
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Lys Glu Glu Val Asp Arg His Leu Gln Cys Arg Ala Pro Arg Asp Leu		
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Cys Glu Arg Met Ala Ala Ala Leu Arg Glu Ser Pro Gly Ala Ser Phe		
225	230	235 240
Arg Gly Ile Ser Ala Asp His Phe Glu Ala Glu Val Val Glu Arg Thr		
	245	250 255
Asp Val Tyr Tyr Tyr Glu Thr Arg Pro Ala Leu Phe Tyr Arg Val Tyr		
	260	265 270
Val Arg Ser Gly Arg Val Leu Ser Tyr Leu Cys Asp Asn Phe Cys Pro		
	275	280 285
Ala Ile Lys Lys Tyr Glu Gly Gly Val Asp Ala Thr Thr Arg Phe Ile		
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Leu Asp Asn Pro Gly Phe Val Thr Phe Gly Trp Tyr Arg Leu Lys Pro		
305	310	315 320
Gly Arg Asn Asn Thr Leu Ala Gln Pro Arg Ala Pro Met Ala Phe Gly		
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Thr Ser Ser Asp Val Glu Phe Asn Cys Thr Ala Asp Asn Leu Ala Ile		
	340	345 350
Glu Gly Gly Met Ser Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe Asp		
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Ile Glu Cys Lys Ala Gly Gly Glu Asp Glu Leu Ala Phe Pro Val Ala		
	370	375 380
Gly His Pro Glu Asp Leu Val Ile Gln Ile Ser Cys Leu Leu Tyr Asp		
385	390	395 400
Leu Ser Thr Thr Ala Leu Glu His Val Leu Leu Phe Ser Leu Gly Ser		
	405	410 415
Cys Asp Leu Pro Glu Ser His Leu Asn Glu Leu Ala Ala Arg Gly Leu		
	420	425 430
Pro Thr Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu Leu		
	435	440 445
Ala Phe Met Thr Leu Val Lys Gln Tyr Gly Pro Glu Phe Val Thr Gly		
	450	455 460

Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Leu Leu Ala Lys Leu Thr
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 Asp Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly Arg
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 Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys Arg
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 785 790 795 800

Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys Val Val Cys Asn Ser
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 Val Tyr Gly Phe Thr Gly Ala Gln His Gly Leu Leu Pro Cys Leu His
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 Arg Glu Tyr Val His Ala Arg Trp Ala Ala Phe Glu Gln Leu Leu Ala
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 Asp Phe Pro Glu Ala Ala Asp Met Arg Ala Pro Gly Pro Tyr Ser Met
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 Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe Val Leu Cys Arg Gly
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 Leu Thr Ala Ala Gly Leu Thr Ala Met Gly Asp Lys Met Ala Ser His
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 Ile Ser Arg Ala Leu Phe Leu Pro Pro Ile Lys Leu Glu Cys Glu Lys
 915 920 925
 Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys Lys Tyr Ile Gly Val
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 Ile Tyr Gly Gly Lys Met Leu Ile Lys Gly Val Asp Leu Val Arg Lys
 945 950 955 960
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 965 970 975
 Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala Ala Ala Leu Ala Glu
 980 985 990
 Arg Pro Ala Glu Glu Trp Leu Ala Arg Pro Leu Pro Glu Gly Leu Gln
 995 1000 1005
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 Pro Glu Arg Asp Ile Gln Asp Phe Val Leu Thr Ala Glu Leu Ser
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 Arg His Pro Arg Ala Tyr Thr Asn Lys Arg Leu Ala His Leu Thr
 1040 1045 1050
 Val Tyr Tyr Lys Leu Met Ala Arg Arg Ala Gln Val Pro Ser Ile
 1055 1060 1065
 Lys Asp Arg Ile Pro Tyr Val Ile Val Ala Gln Thr Arg Glu Val
 1070 1075 1080
 Glu Glu Thr Val Ala Arg Leu Ala Ala Leu Arg Glu Leu Asp Ala
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 Ala Ala Pro Gly Asp Glu Pro Ala Pro Pro Ala Ala Leu Pro Ser
 1100 1105 1110
 Pro Ala Lys Arg Pro Arg Glu Thr Pro Ser His Ala Asp Pro Pro

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Glu Asp Pro Ala Tyr Ala Ile Ala His Gly Val Ala Leu Asn Thr		
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Asp Tyr Tyr Phe Ser His Leu Leu Gly Ala Ala Cys Val Thr Phe		
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Lys Ala Leu Phe Gly Asn Asn Ala Lys Ile Thr Glu Ser Leu Leu		
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Lys Arg Phe Ile Pro Glu Val Trp His Pro Pro Asp Asp Val Ala		
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Ala Arg Leu Arg Ala Ala Gly Phe Gly Ala Val Gly Ala Gly Ala		
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<210> 7
 <211> 3708
 <212> DNA
 <213> herpes simplex

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<210> 8
<211> 1235
<212> PRT
<213> herpes simplex

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<400> 8

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20          25          30
Gly Arg Gly Pro Pro Pro Cys Leu Arg Gln Asn Phe Tyr Asn Pro Tyr
35          40          45
Leu Ala Pro Val Gly Thr Gln Gln Lys Pro Thr Gly Pro Thr Gln Arg
50          55          60
His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro Arg
65          70          75          80
Val Leu Asp Glu Asp Ala Pro Pro Glu Lys Arg Ala Gly Val His Asp
85          90          95
Gly His Leu Lys Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu Arg
100         105         110
Asp Val Leu Arg Val Gly Ser Gly Gly Phe Trp Pro Arg Arg Ser Arg

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Gly	Met	Arg	Ala	Ala	Gln	Phe	His	Ala	Arg	Phe	Met	Asp	Ala	Ile	Thr
			165						170					175	
Pro	Thr	Gly	Thr	Val	Ile	Thr	Leu	Leu	Gly	Leu	Thr	Pro	Glu	Gly	His
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Arg	Val	Ala	Val	His	Val	Tyr	Gly	Thr	Arg	Gln	Tyr	Phe	Tyr	Met	Asn
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Lys	Glu	Glu	Val	Asp	Arg	His	Leu	Gln	Cys	Arg	Ala	Pro	Arg	Asp	Leu
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Cys	Glu	Arg	Met	Ala	Ala	Ala	Leu	Arg	Glu	Ser	Pro	Gly	Ala	Ser	Phe
225				230					235						240
Arg	Gly	Ile	Ser	Ala	Asp	His	Phe	Glu	Ala	Glu	Val	Val	Glu	Arg	Thr
			245					250						255	
Asp	Val	Tyr	Tyr	Tyr	Glu	Thr	Arg	Pro	Ala	Leu	Phe	Tyr	Arg	Val	Tyr
		260					265						270		
Val	Arg	Ser	Gly	Arg	Val	Leu	Ser	Tyr	Leu	Cys	Asp	Asn	Phe	Cys	Pro
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Ala	Ile	Lys	Lys	Tyr	Glu	Gly	Gly	Val	Asp	Ala	Thr	Thr	Arg	Phe	Ile
	290					295					300				
Leu	Asp	Asn	Pro	Gly	Phe	Val	Thr	Phe	Gly	Trp	Tyr	Arg	Leu	Lys	Pro
305				310					315						320
Gly	Arg	Asn	Asn	Thr	Leu	Ala	Gln	Pro	Arg	Ala	Pro	Met	Ala	Phe	Gly
			325					330					335		
Thr	Ser	Ser	Asp	Val	Glu	Phe	Asn	Cys	Thr	Ala	Asp	Asn	Leu	Ala	Ile
		340					345						350		
Glu	Gly	Gly	Met	Ser	Asp	Leu	Pro	Ala	Tyr	Lys	Leu	Met	Cys	Phe	Asp
	355					360					365				
Ile	Glu	Cys	Lys	Ala	Gly	Gly	Glu	Asp	Glu	Leu	Ala	Phe	Pro	Val	Ala
	370					375					380				
Gly	His	Pro	Glu	Asp	Leu	Val	Ile	Gln	Ile	Ser	Cys	Leu	Leu	Tyr	Asp
385				390					395						400
Leu	Ser	Thr	Thr	Ala	Leu	Glu	His	Val	Leu	Leu	Phe	Ser	Leu	Gly	Ser
			405					410					415		
Cys	Asp	Leu	Pro	Glu	Ser	His	Leu	Asn	Glu	Leu	Ala	Ala	Arg	Gly	Leu
		420					425						430		
Pro	Thr	Pro	Val	Val	Leu	Glu	Phe	Asp	Ser	Glu	Phe	Glu	Met	Leu	Leu
	435					440					445				

23

Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser Ser Pro Glu Glu Ala
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 Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys Val Val Cys Asn Ser
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 Val Tyr Gly Phe Thr Gly Ala Gln His Gly Leu Leu Pro Cys Leu His
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 Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu Met Leu Leu Ala Thr
 835 840 845
 Arg Glu Tyr Val His Ala Arg Trp Ala Ala Phe Glu Gln Leu Leu Ala
 850 855 860
 Asp Phe Pro Glu Ala Ala Asp Met Arg Ala Pro Gly Pro Tyr Ser Met
 865 870 875 880
 Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe Val Leu Cys Arg Gly
 885 890 895
 Leu Thr Ala Ala Gly Leu Thr Ala Val Gly Asp Lys Met Ala Ser His
 900 905 910
 Ile Ser Arg Ala Leu Phe Leu Ser Pro Ile Lys Leu Glu Cys Glu Lys
 915 920 925
 Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys Lys Tyr Ile Gly Val
 930 935 940
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 945 950 955 960
 Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg Ala Leu Val Asp Leu
 965 970 975
 Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala Ala Ala Leu Ala Glu
 980 985 990
 Arg Pro Ala Glu Glu Trp Leu Ala Arg Pro Leu Pro Glu Gly Leu Gln
 995 1000 1005
 Ala Phe Gly Ala Val Leu Val Asp Ala His Arg Arg Ile Thr Asp
 1010 1015 1020
 Pro Glu Arg Asp Ile Gln Asp Phe Val Leu Thr Ala Glu Leu Ser
 1025 1030 1035
 Arg His Pro Arg Ala Tyr Thr Asn Lys Arg Leu Ala His Leu Thr
 1040 1045 1050
 Val Tyr Tyr Lys Leu Met Ala Arg Arg Ala Gln Val Pro Ser Ile
 1055 1060 1065
 Lys Asp Arg Ile Pro Tyr Val Ile Val Ala Gln Thr Arg Glu Val
 1070 1075 1080
 Glu Glu Thr Val Ala Arg Leu Ala Ala Leu Arg Glu Leu Asp Ala
 1085 1090 1095
 Ala Ala Pro Gly Asp Glu Pro Ala Pro Pro Ala Ala Leu Pro Ser

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Pro Ala Lys Arg Pro Arg Glu Thr Pro Leu His Ala Asp Pro Pro 1115	1120	1125
Gly Gly Ala Ser Lys Pro Arg Lys Leu Leu Val Ser Glu Leu Ala 1130	1135	1140
Glu Asp Pro Ala Tyr Ala Ile Ala His Gly Val Ala Leu Asn Thr 1145	1150	1155
Asp Tyr Tyr Phe Ser His Leu Leu Gly Ala Ala Cys Val Thr Phe 1160	1165	1170
Lys Ala Leu Phe Gly Asn Asn Ala Lys Ile Thr Glu Ser Leu Leu 1175	1180	1185
Lys Arg Phe Ile Pro Glu Val Trp His Pro Pro Asp Asp Val Ala 1190	1195	1200
Ala Arg Leu Arg Ala Ala Gly Phe Gly Ala Val Gly Ala Gly Ala 1205	1210	1215
Thr Ala Glu Glu Thr Arg Arg Met Leu His Arg Ala Phe Asp Thr 1220	1225	1230
Leu Ala 1235		

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 <211> 3708
 <212> DNA
 <213> herpes simplex

<400> 9
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<210> 10
 <211> 1235
 <212> PRT
 <213> herpes simplex

<400> 10

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Met Phe Ser Gly Gly Gly Gly Pro Leu Ser Pro Gly Gly Lys Ser Ala
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          20           25           30

Gly Arg Gly Pro Pro Pro Cys Leu Arg Gln Asn Phe Tyr Asn Pro Tyr
          35           40           45

Leu Ala Pro Val Gly Thr Gln Gln Lys Pro Thr Gly Pro Thr Gln Arg
          50           55           60

His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro Arg
65           70           75           80

Val Leu Asp Glu Asp Ala Pro Pro Glu Lys Arg Ala Gly Val His Asp
          85           90           95

Gly His Leu Lys Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu Arg

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100					105					110						
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Leu	Trp	Gly	Gly	Val	Asp	His	Ala	Pro	Ala	Gly	Phe	Asn	Pro	Thr	Val	
130					135					140						
Thr	Val	Phe	His	Val	Tyr	Asp	Ile	Leu	Glu	Asn	Val	Glu	His	Ala	Tyr	
145					150					155					160	
Gly	Met	Arg	Ala	Ala	Gln	Phe	His	Ala	Arg	Phe	Met	Asp	Ala	Ile	Thr	
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Pro	Thr	Gly	Thr	Val	Ile	Thr	Leu	Leu	Gly	Leu	Thr	Pro	Glu	Gly	His	
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Arg	Val	Ala	Val	His	Val	Tyr	Gly	Thr	Arg	Gln	Tyr	Phe	Tyr	Met	Asn	
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Cys	Glu	Arg	Met	Ala	Ala	Ala	Leu	Arg	Glu	Ser	Pro	Gly	Ala	Ser	Phe	
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Arg	Gly	Ile	Ser	Ala	Asp	His	Phe	Glu	Ala	Glu	Val	Val	Glu	Arg	Thr	
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Asp	Val	Tyr	Tyr	Tyr	Glu	Thr	Arg	Pro	Ala	Leu	Phe	Tyr	Arg	Val	Tyr	
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Val	Arg	Ser	Gly	Arg	Val	Leu	Ser	Tyr	Leu	Cys	Asp	Asn	Phe	Cys	Pro	
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Gly	Arg	Asn	Asn	Thr	Leu	Ala	Gln	Pro	Arg	Ala	Pro	Met	Ala	Phe	Gly	
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Thr	Ser	Ser	Asp	Val	Glu	Phe	Asn	Cys	Thr	Ala	Asp	Asn	Leu	Ala	Ile	
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Glu	Gly	Gly	Met	Ser	Asp	Leu	Pro	Ala	Tyr	Lys	Leu	Met	Cys	Phe	Asp	
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Ile	Glu	Cys	Lys	Ala	Gly	Gly	Glu	Asp	Glu	Leu	Ala	Phe	Pro	Val	Ala	
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Gly	His	Pro	Glu	Asp	Leu	Val	Ile	Gln	Ile	Ser	Cys	Leu	Leu	Tyr	Asp	
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Leu	Ser	Thr	Thr	Ala	Leu	Glu	His	Val	Leu	Leu	Phe	Ser	Leu	Gly	Ser	
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Cys	Asp	Leu	Pro	Glu	Ser	His	Leu	Asn	Glu	Leu	Ala	Ala	Arg	Gly	Leu	
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Pro Thr Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu Leu
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 980 985 990
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Gly Gly Ala Ser Lys Pro Arg	Lys Leu Leu Val Ser	Glu Leu Ala
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Glu Asp Pro Ala Tyr Ala Ile	Ala His Gly Val Ala	Leu Asn Thr
1145	1150	1155
Asp Tyr Tyr Phe Ser His Leu	Leu Gly Ala Ala Cys	Val Thr Phe
1160	1165	1170
Lys Ala Leu Phe Gly Asn Asn	Ala Lys Ile Thr Glu	Ser Leu Leu
1175	1180	1185
Lys Arg Phe Ile Pro Glu Val	Trp His Pro Pro Asp	Asp Val Ala
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Ala Arg Leu Arg Thr Ala Gly	Phe Gly Ala Val Gly	Ala Gly Ala
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Leu Ala		
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 <213> herpes simplex

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cgggtggagg cgcggtcat ctacggggac acggacagcg tgtttgccg ctttcgtggc 2760
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Gly Lys Arg Pro Pro Gln Lys Gln Phe Leu Gln Ile Val Pro Arg Gly
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Val Met Phe Asp Gly Gln Thr Gly Leu Ile Lys His Lys Thr Gly Arg
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Leu Pro Leu Met Phe Tyr Arg Glu Ile Lys His Leu Leu Ser His Asp
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Met Val Trp Pro Cys Pro Trp Arg Glu Thr Leu Val Gly Arg Val Val
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 Gly Pro Ile Arg Phe His Thr Tyr Asp Gln Thr Asp Ala Val Leu Phe
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 Phe Asp Ser Pro Glu Asn Val Ser Pro Arg Tyr Arg Gln His Leu Val
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 Pro Ser Gly Asn Val Leu Arg Phe Phe Gly Ala Thr Glu His Gly Tyr
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 Ser Ile Cys Val Asn Val Phe Gly Gln Arg Ser Tyr Phe Tyr Cys Glu
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 Tyr Ser Asp Thr Asp Arg Leu Arg Glu Val Ile Ala Ser Val Gly Glu
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 Leu Val Pro Glu Pro Arg Thr Pro Tyr Ala Val Ser Val Thr Pro Ala
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 Thr Lys Thr Ser Ile Tyr Gly Tyr Gly Thr Arg Pro Val Pro Asp Leu
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 Gln Cys Val Ser Ile Ser Asn Trp Thr Met Ala Arg Lys Ile Gly Glu
 210 215 220
 Tyr Leu Leu Glu Gln Gly Phe Pro Val Tyr Glu Val Arg Val Asp Pro
 225 230 235 240
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 260 265 270
 Asp Ile Glu Val Asp Cys Asp Val Ser Asp Leu Val Ala Val Pro Asp
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 Asp Ser Ser Trp Pro Arg Tyr Arg Cys Leu Ser Phe Asp Ile Glu Cys
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 Met Ser Gly Glu Gly Gly Phe Pro Cys Ala Glu Lys Ser Asp Asp Ile
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 325 330 335
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 Glu Gly Val Ile Phe Gly His Ser Gly Leu His Leu Phe Thr Ile Gly
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 Thr Cys Gly Gln Val Gly Pro Asp Val Asp Val Tyr Glu Phe Pro Ser
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 Glu Tyr Glu Leu Leu Leu Gly Phe Met Leu Phe Phe Gln Arg Tyr Ala
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Ala	Val	Gly	Phe	Lys	Arg	Gln	Tyr	Ala	Ala	Ala	Phe	Pro	Ser	Ala	Ser	
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His	Asn	Asn	Pro	Ala	Ser	Thr	Ala	Ala	Thr	Lys	Val	Tyr	Ile	Ala	Gly	
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Ser	Val	Val	Ile	Asp	Met	Tyr	Pro	Val	Cys	Met	Ala	Lys	Thr	Asn	Ser	
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Pro	Asn	Tyr	Lys	Leu	Asn	Thr	Met	Ala	Glu	Leu	Tyr	Leu	Arg	Gln	Arg	
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Leu	Val	Arg	Asp	Leu	Phe	Asn	Thr	Ile	Asn	Phe	His	Tyr	Glu	Ala	Gly	
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Leu	Tyr	Pro	Ser	Ile	Ile	Met	Ala	His	Asn	Leu	Cys	Tyr	Ser	Thr	Leu	
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 Arg Ala Val Arg Glu Cys Met Arg Glu Cys Gln Asp Pro Val Arg Arg
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 930 935 940
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 Pro Ser Tyr Val Arg Glu His Gly Val Pro Ile His Ala Asp Lys
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 Met Val Trp Pro Cys Pro Trp Arg Glu Thr Leu Val Gly Arg Val Val
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 Tyr Ser Asp Thr Asp Arg Leu Arg Glu Val Ile Ala Ser Val Gly Glu
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 Asp Ser Ser Trp Pro Arg Tyr Arg Cys Leu Ser Phe Asp Ile Glu Cys
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 Met Ser Gly Glu Gly Gly Phe Pro Cys Ala Glu Lys Ser Asp Asp Ile
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 Val Asp Gln Gly Ile Pro Asn Gly Asn Asp Gly Arg Gly Cys Thr Ser
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 Glu Gly Val Ile Phe Gly His Ser Gly Leu His Leu Phe Thr Ile Gly
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 Glu Tyr Glu Leu Leu Leu Gly Phe Met Leu Phe Phe Gln Arg Tyr Ala
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 Pro Ala Phe Val Thr Gly Tyr Asn Ile Asn Ser Phe Asp Leu Lys Tyr
 405 410 415
 Ile Leu Thr Arg Leu Glu Tyr Leu Tyr Lys Val Asp Ser Gln Arg Phe
 420 425 430

Cys Lys Leu Pro Thr Ala Gln Gly Gly Arg Phe Phe Leu His Ser Pro
 435 440 445
 Ala Val Gly Phe Lys Arg Gln Tyr Ala Ala Ala Phe Pro Ser Ala Ser
 450 455 460
 His Asn Asn Pro Ala Ser Thr Ala Ala Thr Lys Val Tyr Ile Ala Gly
 465 470 475 480
 Ser Val Val Ile Asp Met Tyr Pro Val Cys Met Ala Lys Thr Asn Ser
 485 490 495
 Pro Asn Tyr Lys Leu Asn Thr Met Ala Glu Leu Tyr Leu Arg Gln Arg
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 Lys Asp Asp Leu Ser Tyr Lys Asp Ile Pro Arg Cys Phe Val Ala Asn
 515 520 525
 Ala Glu Gly Arg Ala Gln Val Gly Arg Tyr Cys Leu Gln Asp Ala Val
 530 535 540
 Leu Val Arg Asp Leu Phe Asn Thr Ile Asn Phe His Tyr Glu Ala Gly
 545 550 555 560
 Ala Ile Ala Arg Leu Ala Lys Ile Pro Leu Arg Arg Val Ile Phe Asp
 565 570 575
 Gly Gln Gln Ile Arg Ile Tyr Thr Ser Leu Leu Asp Glu Cys Ala Cys
 580 585 590
 Arg Asp Phe Ile Leu Pro Asn His Tyr Ser Lys Gly Thr Thr Val Pro
 595 600 605
 Glu Thr Asn Ser Val Ala Val Ser Pro Asn Ala Ala Ile Ile Ser Thr
 610 615 620
 Ala Ala Val Pro Gly Asp Ala Gly Ser Val Ala Ala Met Phe Gln Met
 625 630 635 640
 Ser Pro Pro Leu Gln Ser Ala Pro Ser Ser Gln Asp Gly Val Ser Pro
 645 650 655
 Gly Ser Gly Ser Asn Ser Ser Ser Ser Val Gly Val Phe Ser Val Gly
 660 665 670
 Ser Gly Ser Ser Gly Gly Val Gly Val Ser Asn Asp Asn His Gly Ala
 675 680 685
 Gly Gly Thr Ala Ala Val Ser Tyr Gln Gly Ala Thr Val Phe Glu Pro
 690 695 700
 Glu Val Gly Tyr Tyr Asn Asp Pro Val Ala Val Phe Asp Phe Ala Ser
 705 710 715 720
 Leu Tyr Pro Ser Ile Ile Met Ala His Asn Leu Cys Tyr Ser Thr Leu
 725 730 735
 Leu Val Pro Gly Gly Glu Tyr Pro Val Asp Pro Ala Asp Val Tyr Ser
 740 745 750
 Val Thr Leu Glu Asn Gly Val Thr His Arg Phe Val Arg Ala Ser Val

755					760					765					
Arg	Val	Ser	Val	Leu	Ser	Glu	Leu	Leu	Asn	Lys	Trp	Val	Ser	Gln	Arg
770						775					780				
Arg	Ala	Val	Arg	Glu	Cys	Met	Arg	Glu	Cys	Gln	Asp	Pro	Val	Arg	Arg
785						790					795				800
Met	Leu	Leu	Asp	Lys	Glu	Gln	Met	Ala	Leu	Lys	Val	Thr	Cys	Asn	Ala
				805					810					815	
Phe	Tyr	Gly	Phe	Thr	Gly	Val	Val	Asn	Gly	Met	Met	Pro	Cys	Leu	Pro
			820					825						830	
Ile	Ala	Ala	Ser	Ile	Thr	Arg	Ile	Gly	Arg	Asp	Met	Leu	Glu	Arg	Thr
			835					840						845	
Ala	Arg	Phe	Ile	Lys	Asp	Asn	Phe	Ser	Glu	Pro	Cys	Phe	Leu	His	Asn
						855					860				
Phe	Phe	Asn	Gln	Glu	Asp	Tyr	Val	Val	Gly	Thr	Arg	Glu	Gly	Asp	Ser
865						870					875				880
Glu	Glu	Ser	Ser	Ala	Leu	Pro	Glu	Gly	Leu	Glu	Thr	Ser	Ser	Gly	Gly
				885					890					895	
Ser	Asn	Glu	Arg	Arg	Val	Glu	Ala	Arg	Val	Ile	Tyr	Gly	Asp	Thr	Asp
			900					905						910	
Ser	Val	Phe	Val	Arg	Phe	Arg	Gly	Leu	Thr	Pro	Gln	Ala	Leu	Val	Ala
			915					920						925	
Arg	Gly	Pro	Ser	Leu	Ala	His	Tyr	Val	Thr	Ala	Cys	Leu	Phe	Val	Glu
						935					940				
Pro	Val	Lys	Leu	Glu	Phe	Glu	Lys	Val	Phe	Val	Ser	Leu	Met	Met	Ile
945						950					955				960
Cys	Lys	Lys	Arg	Tyr	Ile	Gly	Lys	Val	Glu	Gly	Ala	Ser	Gly	Leu	Ser
				965					970					975	
Met	Lys	Gly	Val	Asp	Leu	Val	Arg	Lys	Thr	Ala	Cys	Glu	Phe	Val	Lys
			980					985						990	
Gly	Val	Thr	Arg	Asp	Val	Leu	Ser	Leu	Leu	Phe	Glu	Asp	Arg	Glu	Val
			995					1000						1005	
Ser	Glu	Ala	Ala	Val	Arg	Leu	Ser	Arg	Leu	Ser	Leu	Asp	Glu	Val	
						1015					1020				
Lys	Lys	Tyr	Gly	Val	Pro	Arg	Gly	Phe	Trp	Arg	Ile	Leu	Arg	Arg	
						1030					1035				
Leu	Val	Gln	Ala	Arg	Asp	Asp	Leu	Tyr	Leu	His	Arg	Val	Arg	Val	
						1045					1050				
Glu	Asp	Leu	Val	Leu	Ser	Ser	Val	Leu	Ser	Lys	Asp	Ile	Ser	Leu	
						1060					1065				
Tyr	Arg	Gln	Ser	Asn	Leu	Pro	His	Ile	Ala	Val	Ile	Lys	Arg	Leu	
						1075					1080				

Ala Ala Arg Ser Glu Glu Leu Pro Ser Val Gly Asp Arg Val Phe
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 Tyr Val Leu Thr Ala Pro Gly Val Arg Thr Ala Pro Gln Gly Ser
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 Ser Asp Asn Gly Asp Ser Val Thr Ala Gly Val Val Ser Arg Ser
 1115 1120 1125
 Asp Ala Ile Asp Gly Thr Asp Asp Asp Ala Asp Gly Gly Gly Val
 1130 1135 1140
 Glu Glu Ser Asn Arg Arg Gly Gly Glu Pro Ala Lys Lys Arg Ala
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 Arg Lys Pro Pro Ser Ala Val Cys Asn Tyr Glu Val Ala Glu Asp
 1160 1165 1170
 Pro Ser Tyr Val Arg Glu His Gly Val Pro Ile His Ala Asp Lys
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 Tyr Phe Glu Gln Val Leu Lys Ala Val Thr Asn Val Leu Ser Pro
 1190 1195 1200
 Val Phe Pro Gly Gly Glu Thr Ala Arg Lys Asp Lys Phe Leu His
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 35 40 45
 His Leu Ala Gln Thr Gly Thr Gln Pro Lys Ala Pro Gly Pro Ala Gln
 50 55 60
 Arg His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro
 65 70 75 80
 Arg Ser Leu Asp Glu Asp Ala Pro Ala Glu Gln Arg Thr Gly Val His
 85 90 95
 Asp Gly Arg Leu Arg Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu
 100 105 110
 Arg Asp Val Leu Arg Val Gly Pro Glu Gly Phe Trp Pro Arg Arg Leu

115					120					125					
Arg	Leu	Trp	Gly	Gly	Ala	Asp	His	Ala	Pro	Lys	Gly	Phe	Asp	Pro	Thr
130						135					140				
Val	Thr	Val	Phe	His	Val	Tyr	Asp	Ile	Leu	Glu	His	Val	Glu	His	Ala
145					150					155					160
Tyr	Ser	Met	Arg	Ala	Ala	Gln	Leu	His	Glu	Arg	Phe	Met	Asp	Ala	Ile
				165					170					175	
Thr	Pro	Ala	Gly	Thr	Val	Ile	Thr	Leu	Leu	Gly	Leu	Thr	Pro	Glu	Gly
			180					185					190		
His	Arg	Val	Ala	Val	His	Val	Tyr	Gly	Thr	Arg	Gln	Tyr	Phe	Tyr	Met
		195					200					205			
Asn	Lys	Ala	Glu	Val	Asp	Arg	His	Leu	Gln	Cys	Arg	Ala	Pro	Arg	Asp
210						215					220				
Leu	Cys	Glu	Arg	Leu	Ala	Ala	Ala	Leu	Arg	Glu	Ser	Pro	Gly	Ala	Ser
225					230					235					240
Phe	Arg	Gly	Ile	Ser	Ala	Asp	His	Phe	Glu	Ala	Glu	Val	Val	Glu	Arg
				245					250					255	
Ala	Asp	Val	Tyr	Tyr	Tyr	Glu	Thr	Arg	Pro	Thr	Leu	Tyr	Tyr	Arg	Val
			260					265					270		
Phe	Val	Arg	Ser	Gly	Arg	Ala	Leu	Ala	Tyr	Leu	Cys	Asp	Asn	Phe	Cys
		275					280					285			
Pro	Ala	Ile	Arg	Lys	Tyr	Glu	Gly	Gly	Val	Asp	Ala	Thr	Thr	Arg	Phe
		290				295					300				
Ile	Leu	Asp	Asn	Pro	Gly	Phe	Val	Thr	Phe	Gly	Trp	Tyr	Arg	Leu	Lys
305					310					315					320
Pro	Gly	Arg	Gly	Asn	Ala	Pro	Ala	Gln	Pro	Arg	Pro	Pro	Thr	Ala	Phe
				325					330					335	
Gly	Thr	Ser	Ser	Asp	Val	Glu	Phe	Asn	Cys	Thr	Ala	Asp	Asn	Leu	Ala
			340					345					350		
Val	Glu	Gly	Ala	Met	Cys	Asp	Leu	Pro	Ala	Tyr	Lys	Leu	Met	Cys	Phe
		355					360					365			
Asp	Ile	Glu	Cys	Lys	Ala	Gly	Gly	Glu	Asp	Glu	Leu	Ala	Phe	Pro	Val
		370				375					380				
Ala	Glu	Arg	Pro	Glu	Asp	Leu	Val	Ile	Gln	Ile	Ser	Cys	Leu	Leu	Tyr
385					390					395					400
Asp	Leu	Ser	Thr	Thr	Ala	Leu	Glu	His	Ile	Leu	Leu	Phe	Ser	Leu	Gly
				405					410					415	
Ser	Cys	Asp	Leu	Pro	Glu	Ser	His	Leu	Ser	Asp	Leu	Ala	Ser	Arg	Gly
			420					425					430		
Leu	Pro	Ala	Pro	Val	Val	Leu	Glu	Phe	Asp	Ser	Glu	Phe	Glu	Met	Leu
		435					440					445			

Leu Ala Phe Met Thr Phe Val Lys Gln Tyr Gly Pro Glu Phe Val Thr
 450 455 460
 Gly Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Val Leu Thr Lys Leu
 465 470 475 480
 Thr Glu Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly
 485 490 495
 Arg Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys
 500 505 510
 Arg Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly
 515 520 525
 Ile Ile Thr Asp Lys Val Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val
 530 535 540
 Ala Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp
 545 550 555 560
 Ile Pro Ala Tyr Tyr Ala Ser Gly Pro Ala Gln Arg Gly Val Ile Gly
 565 570 575
 Glu Tyr Cys Val Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys
 580 585 590
 Phe Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile
 595 600 605
 Asn Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr
 610 615 620
 Cys Leu Leu Arg Leu Ala Gly Gln Lys Gly Phe Ile Leu Pro Asp Thr
 625 630 635 640
 Gln Gly Arg Phe Arg Gly Leu Asp Lys Glu Ala Pro Lys Arg Pro Ala
 645 650 655
 Val Pro Arg Gly Glu Gly Glu Arg Pro Gly Asp Gly Asn Gly Asp Glu
 660 665 670
 Asp Lys Asp Asp Asp Glu Asp Glu Asp Gly Asp Glu Arg Glu Glu Val
 675 680 685
 Ala Arg Glu Thr Gly Gly Arg His Val Gly Tyr Gln Gly Ala Arg Val
 690 695 700
 Leu Asp Pro Thr Ser Gly Phe His Val Asp Pro Val Val Val Phe Asp
 705 710 715 720
 Phe Ala Ser Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu Cys Phe
 725 730 735
 Ser Thr Leu Ser Leu Arg Pro Glu Ala Val Ala His Leu Glu Ala Asp
 740 745 750
 Arg Asp Tyr Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe Phe Val
 755 760 765
 Lys Ala His Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg Asp Trp
 770 775 780

Leu Ala Met Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser Thr Pro
 785 790 795 800
 Glu Glu Ala Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys Val Val
 805 810 815
 Cys Asn Ser Val Tyr Gly Phe Thr Gly Val Gln His Gly Leu Leu Pro
 820 825 830
 Cys Leu His Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu Met Leu
 835 840 845
 Leu Ala Thr Arg Ala Tyr Val His Ala Arg Trp Ala Glu Phe Asp Gln
 850 855 860
 Leu Leu Ala Asp Phe Pro Glu Ala Ala Gly Met Arg Ala Pro Gly Pro
 865 870 875 880
 Tyr Ser Met Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe Val Leu
 885 890 895
 Cys Arg Gly Leu Thr Ala Ala Gly Leu Val Ala Met Gly Asp Lys Met
 900 905 910
 Ala Ser His Ile Ser Arg Ala Leu Phe Leu Pro Pro Ile Lys Leu Glu
 915 920 925
 Cys Glu Lys Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys Lys Tyr
 930 935 940
 Ile Gly Val Ile Cys Gly Gly Lys Met Leu Ile Lys Gly Val Asp Leu
 945 950 955 960
 Val Arg Lys Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg Ala Leu
 965 970 975
 Val Asp Leu Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala Ala Ala
 980 985 990
 Leu Ala Glu Arg Pro Ala Glu Glu Trp Leu Ala Arg Pro Leu Pro Glu
 995 1000 1005
 Gly Leu Gln Ala Phe Gly Ala Val Leu Val Asp Ala His Arg Arg
 1010 1015 1020
 Ile Thr Asp Pro Glu Arg Asp Ile Gln Asp Phe Val Leu Thr Ala
 1025 1030 1035
 Glu Leu Ser Arg His Pro Arg Ala Tyr Thr Asn Lys Arg Leu Ala
 1040 1045 1050
 His Leu Thr Val Tyr Tyr Lys Leu Met Ala Arg Arg Ala Gln Val
 1055 1060 1065
 Pro Ser Ile Lys Asp Arg Ile Pro Tyr Val Ile Val Ala Gln Thr
 1070 1075 1080
 Arg Glu Val Glu Glu Thr Val Ala Arg Leu Ala Ala Leu Arg Glu
 1085 1090 1095
 Leu Asp Ala Ala Ala Pro Gly Asp Glu Pro Ala Pro Pro Ala Ala

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Leu Pro Ser Pro Ala Lys Arg	Pro Arg Glu Thr Pro	Ser His Ala
1115	1120	1125
Asp Pro Pro Gly Gly Ala Ser	Lys Pro Arg Lys	Leu Leu Val Ser
1130	1135	1140
Glu Leu Ala Glu Asp Pro Gly	Tyr Ala Ile Ala Arg	Gly Val Pro
1145	1150	1155
Leu Asn Thr Asp Tyr Tyr Phe	Ser His Leu Leu Gly	Ala Ala Cys
1160	1165	1170
Val Thr Phe Lys Ala Leu Phe	Gly Asn Asn Ala Lys	Ile Thr Glu
1175	1180	1185
Ser Leu Leu Lys Arg Phe Ile	Pro Glu Thr Trp His	Pro Pro Asp
1190	1195	1200
Asp Val Ala Ala Arg Leu Arg	Ala Ala Gly Phe Gly	Pro Ala Gly
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Thr Gln Thr Ala Pro Pro Pro	Cys Arg Arg Gln Asn Phe	Tyr Asn Pro
35	40	45
His Leu Ala Gln Thr Gly Thr	Gln Pro Lys Ala Pro Gly	Pro Ala Gln
50	55	60
Arg His Thr Tyr Tyr Ser Glu	Cys Asp Glu Phe Arg Phe	Ile Ala Pro
65	70	75
Arg Ser Leu Asp Glu Asp Ala	Pro Ala Glu Gln Arg Thr	Gly Val His
85	90	95
Asp Gly Arg Leu Arg Arg Ala	Pro Lys Val Tyr Cys Gly	Gly Asp Glu
100	105	110
Arg Asp Val Leu Arg Val Gly	Pro Glu Gly Phe Trp Pro	Arg Arg Leu
115	120	125
Arg Leu Trp Gly Gly Ala Asp	His Ala Pro Glu Gly Phe	Asp Pro Thr
130	135	140

Val Thr Val Phe His Val Tyr Asp Ile Leu Glu His Val Glu His Ala
 145 150 155 160
 Tyr Ser Met Arg Ala Ala Gln Leu His Glu Arg Phe Met Asp Ala Ile
 165 170 175
 Thr Pro Ala Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly
 180 185 190
 His Arg Val Ala Val His Val Tyr Gly Thr Arg Gln Tyr Phe Tyr Met
 195 200 205
 Asn Lys Ala Glu Val Asp Arg His Leu Gln Cys Arg Ala Pro Arg Asp
 210 215 220
 Leu Cys Glu Arg Leu Ala Ala Ala Leu Arg Glu Ser Pro Gly Ala Ser
 225 230 235 240
 Phe Arg Gly Ile Ser Ala Asp His Phe Glu Ala Glu Val Val Glu Arg
 245 250 255
 Ala Asp Val Tyr Tyr Tyr Glu Thr Arg Pro Thr Leu Tyr Tyr Arg Val
 260 265 270
 Phe Val Arg Ser Gly Arg Ala Leu Ala Tyr Leu Cys Asp Asn Phe Cys
 275 280 285
 Pro Ala Ile Arg Lys Tyr Glu Gly Gly Val Asp Ala Thr Thr Arg Phe
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 Ile Leu Asp Asn Pro Gly Phe Val Thr Phe Gly Trp Tyr Arg Leu Lys
 305 310 315 320
 Pro Gly Arg Gly Asn Ala Pro Ala Gln Pro Arg Pro Pro Thr Ala Phe
 325 330 335
 Gly Thr Ser Ser Asp Val Glu Phe Asn Cys Thr Ala Asp Asn Leu Ala
 340 345 350
 Val Glu Gly Ala Met Cys Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe
 355 360 365
 Asp Ile Glu Cys Lys Ala Gly Gly Glu Asp Glu Leu Ala Phe Pro Val
 370 375 380
 Ala Glu Arg Pro Glu Asp Leu Val Ile Gln Ile Ser Cys Leu Leu Tyr
 385 390 395 400
 Asp Leu Ser Thr Thr Ala Leu Glu His Ile Leu Leu Phe Ser Leu Gly
 405 410 415
 Ser Cys Asp Leu Pro Glu Ser His Leu Ser Asp Leu Ala Ser Arg Gly
 420 425 430
 Leu Pro Ala Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu
 435 440 445
 Leu Ala Phe Met Thr Phe Val Lys Gln Tyr Gly Pro Glu Phe Val Thr
 450 455 460
 Gly Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Val Leu Thr Lys Leu

465		470		475		480
Thr Glu Ile Tyr	Lys Val Pro Leu Asp	Gly Tyr Gly Arg Met Asn Gly				
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Arg Gly Val Phe	Arg Val Trp Asp Ile	Gly Gln Ser His Phe Gln Lys				
	500		505		510	
Arg Ser Lys Ile Lys Val	Asn Gly Met Val Asn Ile Asp Met Tyr Gly					
	515		520		525	
Ile Ile Thr Asp Lys Val	Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val					
	530		535		540	
Ala Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp						
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Ile Pro Ala Tyr Tyr Ala Ser Gly Pro Ala Gln Arg Gly Val Ile Gly						
	565		570			575
Glu Tyr Cys Val Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys						
	580		585			590
Phe Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile						
	595		600			605
Asn Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr						
	610		615			620
Cys Leu Leu Arg Leu Ala Gly Gln Lys Gly Phe Ile Leu Pro Asp Thr						
625		630		635		640
Gln Gly Arg Phe Arg Gly Leu Asp Lys Glu Ala Pro Lys Arg Pro Ala						
	645		650			655
Val Pro Arg Gly Glu Gly Glu Arg Pro Gly Asp Gly Asn Gly Asp Glu						
	660		665			670
Asp Lys Asp Asp Asp Glu Asp Gly Asp Glu Asp Gly Asp Glu Arg Glu						
	675		680			685
Glu Val Ala Arg Glu Thr Gly Gly Arg His Val Gly Tyr Gln Gly Ala						
	690		695			700
Arg Val Leu Asp Pro Thr Ser Gly Phe His Val Asp Pro Val Val Val						
705		710		715		720
Phe Asp Phe Ala Ser Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu						
	725		730			735
Cys Phe Ser Thr Leu Ser Leu Arg Pro Glu Ala Val Ala His Leu Glu						
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Ala Asp Arg Asp Tyr Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe						
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Phe Val Lys Ala His Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg						
	770		775			780
Asp Trp Leu Ala Met Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser						
785		790		795		800

Pro Pro Glu Glu Ala Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys
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 Val Val Cys Asn Ser Val Tyr Gly Phe Thr Gly Val Gln His Gly Leu
 820 825 830
 Leu Pro Cys Leu His Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu
 835 840 845
 Met Leu Leu Ala Thr Arg Ala Tyr Val His Ala Arg Trp Ala Glu Phe
 850 855 860
 Asp Gln Leu Leu Ala Asp Phe Pro Glu Ala Ala Gly Met Arg Ala Pro
 865 870 875 880
 Gly Pro Tyr Ser Met Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe
 885 890 895
 Val Leu Cys Arg Gly Leu Thr Ala Ala Gly Leu Val Ala Met Gly Asp
 900 905 910
 Lys Met Ala Ser His Ile Ser Arg Ala Leu Phe Leu Pro Pro Ile Lys
 915 920 925
 Leu Glu Cys Glu Lys Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys
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 Lys Tyr Ile Gly Val Ile Cys Gly Gly Lys Met Leu Ile Lys Gly Val
 945 950 955 960
 Asp Leu Val Arg Lys Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg
 965 970 975
 Ala Leu Val Asp Leu Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala
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 Pro Glu Gly Leu Gln Ala Phe Gly Ala Val Leu Val Asp Ala His
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 Thr Ala Glu Leu Ser Arg His Pro Arg Ala Tyr Thr Asn Lys Arg
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 Gln Val Pro Ser Ile Lys Asp Arg Ile Pro Tyr Val Ile Val Ala
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 Arg Glu Leu Asp Ala Ala Ala Pro Gly Asp Glu Pro Ala Pro Pro
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 Ala Ala Leu Pro Ser Pro Ala Lys Arg Pro Arg Glu Thr Pro Ser
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His Ala Asp Pro Pro Gly Gly Ala Ser Lys Pro Arg Lys Leu Leu
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 Val Ser Glu Leu Ala Glu Asp Pro Gly Tyr Ala Ile Ala Arg Gly
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 Val Pro Leu Asn Thr Asp Tyr Tyr Phe Ser His Leu Leu Gly Ala
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 Ala Cys Val Thr Phe Lys Ala Leu Phe Gly Asn Asn Ala Lys Ile
 1175 1180 1185
 Thr Glu Ser Leu Leu Lys Arg Phe Ile Pro Glu Thr Trp His Pro
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 Pro Asp Asp Val Ala Ala Arg Leu Arg Ala Ala Gly Phe Gly Pro
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 35 40 45
 Leu Ala Pro Val Gly Thr Gln Gln Lys Pro Thr Gly Pro Thr Gln Arg
 50 55 60
 His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro Arg
 65 70 75 80
 Val Leu Asp Glu Asp Ala Pro Pro Glu Lys Arg Ala Gly Val His Asp
 85 90 95
 Gly His Leu Lys Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu Arg
 100 105 110
 Asp Val Leu Arg Val Gly Ser Gly Gly Phe Trp Pro Arg Arg Ser Arg
 115 120 125
 Leu Trp Gly Gly Val Asp His Ala Pro Ala Gly Phe Asn Pro Thr Val
 130 135 140
 Thr Val Phe His Val Tyr Asp Ile Leu Glu Asn Val Glu His Ala Tyr
 145 150 155 160

Gly Met Arg Ala Ala Gln Phe His Ala Arg Phe Met Asp Ala Ile Thr
 165 170 175
 Pro Thr Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly His
 180 185 190
 Arg Val Ala Val His Val Tyr Gly Thr Arg Gln Tyr Phe Tyr Met Asn
 195 200 205
 Lys Glu Glu Val Asp Arg His Leu Gln Cys Arg Ala Pro Arg Asp Leu
 210 215 220
 Cys Glu Arg Met Ala Ala Ala Leu Arg Glu Ser Pro Gly Ala Ser Phe
 225 230 235 240
 Arg Gly Ile Ser Ala Asp His Phe Glu Ala Glu Val Val Glu Arg Thr
 245 250 255
 Asp Val Tyr Tyr Tyr Glu Thr Arg Pro Ala Leu Phe Tyr Arg Val Tyr
 260 265 270
 Val Arg Ser Gly Arg Val Leu Ser Tyr Leu Cys Asp Asn Phe Cys Pro
 275 280 285
 Ala Ile Lys Lys Tyr Glu Gly Gly Val Asp Ala Thr Thr Arg Phe Ile
 290 295 300
 Leu Asp Asn Pro Gly Phe Val Thr Phe Gly Trp Tyr Arg Leu Lys Pro
 305 310 315 320
 Gly Arg Asn Asn Thr Leu Ala Gln Pro Arg Ala Pro Met Ala Phe Gly
 325 330 335
 Thr Ser Ser Asp Val Glu Phe Asn Cys Thr Ala Asp Asn Leu Ala Ile
 340 345 350
 Glu Gly Gly Met Ser Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe Asp
 355 360 365
 Ile Glu Cys Lys Ala Gly Gly Glu Asp Glu Leu Ala Phe Pro Val Ala
 370 375 380
 Gly His Pro Glu Asp Leu Val Ile Gln Ile Ser Cys Leu Leu Tyr Asp
 385 390 395 400
 Leu Ser Thr Thr Ala Leu Glu His Val Leu Leu Phe Ser Leu Gly Ser
 405 410 415
 Cys Asp Leu Pro Glu Ser His Leu Asn Glu Leu Ala Ala Arg Gly Leu
 420 425 430
 Pro Thr Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu Leu
 435 440 445
 Ala Phe Met Thr Leu Val Lys Gln Tyr Gly Pro Glu Phe Val Thr Gly
 450 455 460
 Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Leu Leu Ala Lys Leu Thr
 465 470 475 480
 Asp Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly Arg
 485 490 495

Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys Arg
 500 505 510
 Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly Ile
 515 520 525
 Ile Thr Asp Lys Ile Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val Ala
 530 535 540
 Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp Ile
 545 550 555 560
 Pro Ala Tyr Tyr Ala Ala Gly Pro Ala Gln Arg Gly Val Ile Gly Glu
 565 570 575
 Tyr Cys Ile Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys Phe
 580 585 590
 Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile Asn
 595 600 605
 Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr Cys
 610 615 620
 Leu Leu Arg Leu Ala Asp Gln Lys Gly Phe Ile Leu Pro Asp Thr Gln
 625 630 635 640
 Gly Arg Phe Arg Gly Ala Gly Gly Glu Ala Pro Lys Arg Pro Ala Ala
 645 650 655
 Ala Arg Glu Asp Glu Glu Arg Pro Glu Glu Glu Gly Glu Asp Glu Asp
 660 665 670
 Glu Arg Glu Glu Gly Gly Gly Glu Arg Glu Pro Glu Gly Ala Arg Glu
 675 680 685
 Thr Ala Gly Arg His Val Gly Tyr Gln Gly Ala Arg Val Leu Asp Pro
 690 695 700
 Thr Ser Gly Phe His Val Asn Pro Val Val Val Phe Asp Phe Ala Ser
 705 710 715 720
 Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu Cys Phe Ser Thr Leu
 725 730 735
 Ser Leu Arg Ala Asp Ala Val Ala His Leu Glu Ala Gly Lys Asp Tyr
 740 745 750
 Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe Phe Val Lys Ala His
 755 760 765
 Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg Asp Trp Leu Ala Met
 770 775 780
 Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser Ser Pro Glu Glu Ala
 785 790 795 800
 Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys Val Val Cys Asn Ser
 805 810 815
 Val Tyr Gly Phe Thr Gly Val Gln His Gly Leu Leu Pro Cys Leu His

820					825					830						
Val	Ala	Ala	Thr	Val	Thr	Thr	Ile	Gly	Arg	Glu	Met	Leu	Leu	Ala	Thr	
835					840					845						
Arg	Glu	Tyr	Val	His	Ala	Arg	Trp	Ala	Ala	Phe	Glu	Gln	Leu	Leu	Ala	
850					855					860						
Asp	Phe	Pro	Glu	Ala	Ala	Asp	Met	Arg	Ala	Pro	Gly	Pro	Tyr	Ser	Met	
865					870					875					880	
Arg	Ile	Ile	Tyr	Gly	Asp	Thr	Asp	Ser	Ile	Phe	Val	Leu	Cys	Arg	Gly	
885					890					895						
Leu	Thr	Ala	Ala	Gly	Leu	Thr	Ala	Met	Gly	Asp	Lys	Met	Ala	Ser	His	
900					905					910						
Ile	Ser	Arg	Ala	Leu	Phe	Leu	Pro	Pro	Ile	Lys	Leu	Glu	Cys	Glu	Lys	
915					920					925						
Thr	Phe	Thr	Lys	Leu	Leu	Leu	Ile	Ala	Lys	Lys	Lys	Tyr	Ile	Gly	Val	
930					935					940						
Ile	Tyr	Gly	Gly	Lys	Met	Leu	Ile	Lys	Gly	Val	Asp	Leu	Val	Arg	Lys	
945					950					955					960	
Asn	Asn	Cys	Ala	Phe	Ile	Asn	Arg	Thr	Ser	Arg	Ala	Leu	Val	Asp	Leu	
965					970					975						
Leu	Phe	Tyr	Asp	Asp	Thr	Val	Ser	Gly	Ala	Ala	Ala	Ala	Leu	Ala	Glu	
980					985					990						
Arg	Pro	Ala	Glu	Glu	Trp	Leu	Ala	Arg	Pro	Leu	Pro	Glu	Gly	Leu	Gln	
995					1000					1005						
Ala	Phe	Gly	Ala	Val	Leu	Val	Asp	Ala	His	Arg	Arg	Ile	Thr	Asp		
1010					1015					1020						
Pro	Glu	Arg	Asp	Ile	Gln	Asp	Phe	Val	Leu	Thr	Ala	Glu	Leu	Ser		
1025					1030					1035						
Arg	His	Pro	Arg	Ala	Tyr	Thr	Asn	Lys	Arg	Leu	Ala	His	Leu	Thr		
1040					1045					1050						
Val	Tyr	Tyr	Lys	Leu	Met	Ala	Arg	Arg	Ala	Gln	Val	Pro	Ser	Ile		
1055					1060					1065						
Lys	Asp	Arg	Ile	Pro	Tyr	Val	Ile	Val	Ala	Gln	Thr	Arg	Glu	Val		
1070					1075					1080						
Glu	Glu	Thr	Val	Ala	Arg	Leu	Ala	Ala	Leu	Arg	Glu	Leu	Asp	Ala		
1085					1090					1095						
Ala	Ala	Pro	Gly	Asp	Glu	Pro	Ala	Pro	Pro	Ala	Ala	Leu	Pro	Ser		
1100					1105					1110						
Pro	Ala	Lys	Arg	Pro	Arg	Glu	Thr	Pro	Ser	His	Ala	Asp	Pro	Pro		
1115					1120					1125						
Gly	Gly	Ala	Ser	Lys	Pro	Arg	Lys	Leu	Leu	Val	Ser	Glu	Leu	Ala		
1130					1135					1140						

Glu Asp Pro Ala Tyr Ala Ile Ala His Gly Val Ala Leu Asn Thr
 1145 1150 1155
 Asp Tyr Tyr Phe Ser His Leu Leu Gly Ala Ala Cys Val Thr Phe
 1160 1165 1170
 Lys Ala Leu Phe Gly Asn Asn Ala Lys Ile Thr Glu Ser Leu Leu
 1175 1180 1185
 Lys Arg Phe Ile Pro Glu Val Trp His Pro Pro Asp Asp Val Ala
 1190 1195 1200
 Ala Arg Leu Arg Ala Ala Gly Phe Gly Ala Val Gly Ala Gly Ala
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 Thr Ala Glu Glu Thr Arg Arg Met Leu His Arg Ala Phe Asp Thr
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 Leu Ala
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 Gly Arg Gly Pro Pro Pro Cys Leu Arg Gln Asn Phe Tyr Asn Pro Tyr
 35 40 45
 Leu Ala Pro Val Gly Thr Gln Gln Lys Pro Thr Gly Pro Thr Gln Arg
 50 55 60
 His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro Arg
 65 70 75 80
 Val Leu Asp Glu Asp Ala Pro Pro Glu Lys Arg Ala Gly Val His Asp
 85 90 95
 Gly His Leu Lys Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu Arg
 100 105 110
 Asp Val Leu Arg Val Gly Ser Gly Gly Phe Trp Pro Arg Arg Ser Arg
 115 120 125
 Leu Trp Gly Gly Val Asp His Ala Pro Ala Gly Phe Asn Pro Thr Val
 130 135 140
 Thr Val Phe His Val Tyr Asp Ile Leu Glu Asn Val Glu His Ala Tyr
 145 150 155 160
 Gly Met Arg Ala Ala Gln Phe His Ala Arg Phe Met Asp Ala Ile Thr
 165 170 175
 Pro Thr Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly His

180					185					190					
Arg	Val	Ala	Val	His	Val	Tyr	Gly	Thr	Arg	Gln	Tyr	Phe	Tyr	Met	Asn
	195						200					205			
Lys	Glu	Glu	Val	Asp	Arg	His	Leu	Gln	Cys	Arg	Ala	Pro	Arg	Asp	Leu
	210					215					220				
Cys	Glu	Arg	Met	Ala	Ala	Ala	Leu	Arg	Glu	Ser	Pro	Gly	Ala	Ser	Phe
	225				230					235					240
Arg	Gly	Ile	Ser	Ala	Asp	His	Phe	Glu	Ala	Glu	Val	Val	Glu	Arg	Thr
				245					250					255	
Asp	Val	Tyr	Tyr	Tyr	Glu	Thr	Arg	Pro	Ala	Leu	Phe	Tyr	Arg	Val	Tyr
		260						265					270		
Val	Arg	Ser	Gly	Arg	Val	Leu	Ser	Tyr	Leu	Cys	Asp	Asn	Phe	Cys	Pro
		275					280					285			
Ala	Ile	Lys	Lys	Tyr	Glu	Gly	Gly	Val	Asp	Ala	Thr	Thr	Arg	Phe	Ile
	290					295					300				
Leu	Asp	Asn	Pro	Gly	Phe	Val	Thr	Phe	Gly	Trp	Tyr	Arg	Leu	Lys	Pro
	305				310					315					320
Gly	Arg	Asn	Asn	Thr	Leu	Ala	Gln	Pro	Arg	Ala	Pro	Met	Ala	Phe	Gly
				325					330					335	
Thr	Ser	Ser	Asp	Val	Glu	Phe	Asn	Cys	Thr	Ala	Asp	Asn	Leu	Ala	Ile
			340					345					350		
Glu	Gly	Gly	Met	Ser	Asp	Leu	Pro	Ala	Tyr	Lys	Leu	Met	Cys	Phe	Asp
		355					360					365			
Ile	Glu	Cys	Lys	Ala	Gly	Gly	Glu	Asp	Glu	Leu	Ala	Phe	Pro	Val	Ala
	370					375					380				
Gly	His	Pro	Glu	Asp	Leu	Val	Ile	Gln	Ile	Ser	Cys	Leu	Leu	Tyr	Asp
	385				390					395					400
Leu	Ser	Thr	Thr	Ala	Leu	Glu	His	Val	Leu	Leu	Phe	Ser	Leu	Gly	Ser
				405					410					415	
Cys	Asp	Leu	Pro	Glu	Ser	His	Leu	Asn	Glu	Leu	Ala	Ala	Arg	Gly	Leu
			420					425					430		
Pro	Thr	Pro	Val	Val	Leu	Glu	Phe	Asp	Ser	Glu	Phe	Glu	Met	Leu	Leu
		435					440					445			
Ala	Phe	Met	Thr	Leu	Val	Lys	Gln	Tyr	Gly	Pro	Glu	Phe	Val	Thr	Gly
	450					455					460				
Tyr	Asn	Ile	Ile	Asn	Phe	Asp	Trp	Pro	Phe	Leu	Leu	Ala	Lys	Leu	Thr
	465				470					475					480
Asp	Ile	Tyr	Lys	Val	Pro	Leu	Asp	Gly	Tyr	Gly	Arg	Met	Asn	Gly	Arg
				485					490					495	
Gly	Val	Phe	Arg	Val	Trp	Asp	Ile	Gly	Gln	Ser	His	Phe	Gln	Lys	Arg
			500					505					510		

Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly Ile
 515 520 525
 Ile Thr Asp Lys Ile Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val Ala
 530 535 540
 Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp Ile
 545 550 555 560
 Pro Ala Tyr Tyr Ala Ala Gly Pro Ala Gln Arg Gly Val Ile Gly Glu
 565 570 575
 Tyr Cys Ile Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys Phe
 580 585 590
 Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile Asn
 595 600 605
 Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr Cys
 610 615 620
 Leu Leu Arg Leu Ala Asp Gln Lys Gly Phe Ile Leu Pro Asp Thr Gln
 625 630 635 640
 Gly Arg Phe Arg Gly Ala Gly Gly Glu Ala Pro Lys Arg Pro Ala Ala
 645 650 655
 Ala Arg Glu Asp Glu Glu Arg Pro Glu Glu Glu Gly Glu Asp Glu Asp
 660 665 670
 Glu Arg Glu Glu Gly Gly Gly Glu Arg Glu Pro Glu Gly Ala Arg Glu
 675 680 685
 Thr Ala Gly Arg His Val Gly Tyr Gln Gly Ala Arg Val Leu Asp Pro
 690 695 700
 Ile Ser Gly Phe His Val Asn Pro Val Val Val Phe Asp Phe Ala Ser
 705 710 715 720
 Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu Cys Phe Ser Thr Leu
 725 730 735
 Ser Leu Arg Ala Asp Ala Val Ala His Leu Glu Ala Gly Lys Asp Tyr
 740 745 750
 Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe Phe Val Lys Ala His
 755 760 765
 Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg Asp Trp Leu Ala Met
 770 775 780
 Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser Ser Pro Glu Glu Ala
 785 790 795 800
 Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys Val Val Cys Asn Ser
 805 810 815
 Val Tyr Gly Phe Thr Gly Val Gln His Gly Leu Leu Pro Cys Leu His
 820 825 830
 Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu Met Leu Leu Ala Thr
 835 840 845

Arg Glu Tyr Val His Ala Arg Trp Ala Ala Phe Glu Gln Leu Leu Ala
 850 855 860
 Asp Phe Pro Glu Ala Ala Asp Met Arg Ala Pro Gly Pro Tyr Ser Met
 865 870 875 880
 Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe Val Leu Cys Arg Gly
 885 890 895
 Leu Thr Ala Ala Gly Leu Thr Ala Met Gly Asp Lys Met Ala Ser His
 900 905 910
 Ile Ser Arg Ala Leu Phe Leu Pro Pro Ile Lys Leu Glu Cys Glu Lys
 915 920 925
 Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys Lys Tyr Ile Gly Val
 930 935 940
 Ile Tyr Gly Gly Lys Met Leu Ile Lys Gly Val Asp Leu Val Arg Lys
 945 950 955 960
 Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg Ala Leu Val Asp Leu
 965 970 975
 Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala Ala Ala Leu Ala Glu
 980 985 990
 Arg Pro Ala Glu Glu Trp Leu Ala Arg Pro Leu Pro Glu Gly Leu Gln
 995 1000 1005
 Ala Phe Gly Ala Val Leu Val Asp Ala His Arg Arg Ile Thr Asp
 1010 1015 1020
 Pro Glu Arg Asp Ile Gln Asp Phe Val Leu Thr Ala Glu Leu Ser
 1025 1030 1035
 Arg His Pro Arg Ala Tyr Thr Asn Lys Arg Leu Ala His Leu Thr
 1040 1045 1050
 Val Tyr Tyr Lys Leu Met Ala Arg Arg Ala Gln Val Pro Ser Ile
 1055 1060 1065
 Lys Asp Arg Ile Pro Tyr Val Ile Val Ala Gln Thr Arg Glu Val
 1070 1075 1080
 Glu Glu Thr Val Ala Arg Leu Ala Ala Leu Arg Glu Leu Asp Ala
 1085 1090 1095
 Ala Ala Pro Gly Asp Glu Pro Ala Pro Pro Ala Ala Leu Pro Ser
 1100 1105 1110
 Pro Ala Lys Arg Pro Arg Glu Thr Pro Ser Pro Ala Asp Pro Pro
 1115 1120 1125
 Gly Gly Ala Ser Lys Pro Arg Lys Leu Leu Val Ser Glu Leu Ala
 1130 1135 1140
 Glu Asp Pro Ala Tyr Ala Ile Ala His Gly Val Ala Leu Asn Thr
 1145 1150 1155
 Asp Tyr Tyr Phe Ser His Leu Leu Gly Ala Ala Cys Val Thr Phe

1160	1165	1170
Lys Ala Leu Phe Gly Asn Asn Ala Lys Ile Thr Glu Ser Leu Leu		
1175	1180	1185
Lys Arg Phe Ile Pro Glu Val Trp His Pro Pro Asp Asp Val Thr		
1190	1195	1200
Ala Arg Leu Arg Ala Ala Gly Phe Gly Ala Val Gly Ala Gly Ala		
1205	1210	1215
Thr Ala Glu Glu Thr Arg Arg Met Leu His Arg Ala Phe Asp Thr		
1220	1225	1230
Leu Ala		
1235		
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Ala Arg Ala Ala Ser Gly Phe Phe Ala Pro Ala Gly Pro Arg Gly Ala		
	20	25 30
Gly Arg Gly Pro Pro Pro Cys Leu Arg Gln Asn Phe Tyr Asn Pro Tyr		
	35	40 45
Leu Ala Pro Val Gly Thr Gln Gln Lys Pro Thr Gly Pro Thr Gln Arg		
	50	55 60
His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro Arg		
	65	70 75 80
Val Leu Asp Glu Asp Ala Pro Pro Glu Lys Arg Ala Gly Val His Asp		
	85	90 95
Gly His Leu Lys Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu Arg		
	100	105 110
Asp Val Leu Arg Val Gly Ser Gly Gly Phe Trp Pro Arg Arg Ser Arg		
	115	120 125
Leu Trp Gly Gly Val Asp His Ala Pro Ala Gly Phe Asn Pro Thr Val		
	130	135 140
Thr Val Phe His Val Tyr Asp Ile Leu Glu Asn Val Glu His Ala Tyr		
	145	150 155 160
Gly Met Arg Ala Ala Gln Phe His Ala Arg Phe Met Asp Ala Ile Thr		
	165	170 175
Pro Thr Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly His		
	180	185 190
Arg Val Ala Val His Val Tyr Gly Thr Arg Gln Tyr Phe Tyr Met Asn		
	195	200 205

Lys Glu Glu Val Asp Arg His Leu Gln Cys Arg Ala Pro Arg Asp Leu
 210 215 220
 Cys Glu Arg Met Ala Ala Ala Leu Arg Glu Ser Pro Gly Ala Ser Phe
 225 230 235 240
 Arg Gly Ile Ser Ala Asp His Phe Glu Ala Glu Val Val Glu Arg Thr
 245 250 255
 Asp Val Tyr Tyr Tyr Glu Thr Arg Pro Ala Leu Phe Tyr Arg Val Tyr
 260 265 270
 Val Arg Ser Gly Arg Val Leu Ser Tyr Leu Cys Asp Asn Phe Cys Pro
 275 280 285
 Ala Ile Lys Lys Tyr Glu Gly Gly Val Asp Ala Thr Thr Arg Phe Ile
 290 295 300
 Leu Asp Asn Pro Gly Phe Val Thr Phe Gly Trp Tyr Arg Leu Lys Pro
 305 310 315 320
 Gly Arg Asn Asn Thr Leu Ala Gln Pro Arg Ala Pro Met Ala Phe Gly
 325 330 335
 Thr Ser Ser Asp Val Glu Phe Asn Cys Thr Ala Asp Asn Leu Ala Ile
 340 345 350
 Glu Gly Gly Met Ser Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe Asp
 355 360 365
 Ile Glu Cys Lys Ala Gly Gly Glu Asp Glu Leu Ala Phe Pro Val Ala
 370 375 380
 Gly His Pro Glu Asp Leu Val Ile Gln Ile Ser Cys Leu Leu Tyr Asp
 385 390 395 400
 Leu Ser Thr Thr Ala Leu Glu His Val Leu Leu Phe Ser Leu Gly Ser
 405 410 415
 Cys Asp Leu Pro Glu Ser His Leu Asn Glu Leu Ala Ala Arg Gly Leu
 420 425 430
 Pro Thr Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu Leu
 435 440 445
 Ala Phe Met Thr Leu Val Lys Gln Tyr Gly Pro Glu Phe Val Thr Gly
 450 455 460
 Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Leu Leu Ala Lys Leu Thr
 465 470 475 480
 Asp Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly Arg
 485 490 495
 Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys Arg
 500 505 510
 Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly Ile
 515 520 525
 Ile Thr Asp Lys Ile Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val Ala

530					535					540					
Glu	Ala	Val	Leu	Lys	Asp	Lys	Lys	Lys	Asp	Leu	Ser	Tyr	Arg	Asp	Ile
545					550					555					560
Pro	Thr	Tyr	Tyr	Ala	Ala	Gly	Pro	Ala	Gln	Arg	Gly	Val	Ile	Gly	Glu
				565					570					575	
Tyr	Cys	Ile	Gln	Asp	Ser	Leu	Leu	Val	Gly	Gln	Leu	Phe	Phe	Lys	Phe
			580					585					590		
Leu	Pro	His	Leu	Glu	Leu	Ser	Ala	Val	Ala	Arg	Leu	Ala	Gly	Ile	Asn
		595					600					605			
Ile	Thr	Arg	Thr	Ile	Tyr	Asp	Gly	Gln	Gln	Ile	Arg	Val	Phe	Thr	Cys
		610				615					620				
Leu	Leu	Arg	Leu	Ala	Asp	Gln	Lys	Gly	Phe	Ile	Leu	Pro	Asp	Thr	Gln
625					630					635					640
Gly	Arg	Phe	Arg	Gly	Ala	Gly	Gly	Glu	Ala	Pro	Lys	Arg	Pro	Ala	Ala
				645					650					655	
Ala	Arg	Glu	Asp	Glu	Glu	Arg	Pro	Glu	Glu	Glu	Gly	Glu	Asp	Glu	Asn
			660					665					670		
Glu	Arg	Glu	Glu	Gly	Gly	Gly	Glu	Arg	Glu	Pro	Glu	Gly	Ala	Arg	Glu
		675					680					685			
Thr	Ala	Gly	Arg	His	Val	Gly	Tyr	Gln	Gly	Ala	Arg	Val	Leu	Asp	Pro
	690					695					700				
Thr	Ser	Gly	Phe	His	Val	Asn	Pro	Val	Val	Val	Phe	Asp	Phe	Ala	Ser
705					710					715					720
Leu	Tyr	Pro	Ser	Ile	Ile	Gln	Ala	His	Asn	Leu	Cys	Phe	Ser	Thr	Leu
				725					730					735	
Ser	Leu	Arg	Ala	Asp	Ala	Val	Ala	His	Leu	Glu	Ala	Gly	Lys	Asp	Tyr
			740				745						750		
Leu	Glu	Ile	Glu	Val	Gly	Gly	Arg	Arg	Leu	Phe	Phe	Val	Lys	Ala	His
		755					760					765			
Val	Arg	Glu	Ser	Leu	Leu	Ser	Ile	Leu	Leu	Arg	Asp	Trp	Leu	Ala	Met
		770				775					780				
Arg	Lys	Gln	Ile	Arg	Ser	Arg	Ile	Pro	Gln	Ser	Ser	Pro	Glu	Glu	Ala
785					790					795					800
Val	Leu	Leu	Asp	Lys	Gln	Gln	Ala	Ala	Ile	Lys	Val	Val	Cys	Asn	Ser
				805					810					815	
Val	Tyr	Gly	Phe	Thr	Gly	Val	Gln	His	Gly	Leu	Leu	Pro	Cys	Leu	His
			820				825					830			
Val	Ala	Ala	Thr	Val	Thr	Thr	Ile	Gly	Arg	Glu	Met	Leu	Leu	Ala	Thr
		835					840					845			
Arg	Glu	Tyr	Val	His	Ala	Arg	Trp	Ala	Ala	Phe	Glu	Gln	Leu	Leu	Ala
		850				855					860				

Asp Phe Pro Glu Ala Ala Asp Met Arg Ala Pro Gly Pro Tyr Ser Met																			
865					870				875									880	
Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe Val Leu Cys Arg Gly					885				890									895	
Leu Thr Ala Ala Gly Leu Thr Ala Val Gly Asp Lys Met Ala Ser His					900				905									910	
Ile Ser Arg Ala Leu Phe Leu Pro Pro Ile Lys Leu Glu Cys Glu Lys					915				920									925	
Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys Lys Tyr Ile Gly Val								935										940	
Ile Tyr Gly Gly Lys Met Leu Ile Lys Gly Val Asp Leu Val Arg Lys					945				950									955	960
Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg Ala Leu Val Asp Leu									965									970	975
Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala Ala Ala Leu Ala Glu					980													985	990
Arg Pro Ala Glu Glu Trp Leu Ala Arg Pro Leu Pro Glu Gly Leu Gln									995									1000	1005
Ala Phe Gly Ala Val Leu Val Asp Ala His Arg Arg Ile Thr Asp									1010									1015	1020
Pro Glu Arg Asp Ile Gln Asp Phe Val Leu Thr Ala Glu Leu Ser									1025									1030	1035
Arg His Pro Arg Ala Tyr Thr Asn Lys Arg Leu Ala His Leu Thr									1040									1045	1050
Val Tyr Tyr Lys Leu Met Ala Arg Arg Ala Gln Val Pro Ser Ile									1055									1060	1065
Lys Asp Arg Ile Pro Tyr Val Ile Val Ala Gln Thr Arg Glu Val									1070									1075	1080
Glu Glu Thr Val Ala Arg Leu Ala Ala Leu Arg Glu Leu Asp Ala									1085									1090	1095
Ala Ala Pro Gly Asp Glu Pro Ala Pro Pro Ala Ala Leu Pro Ser									1100									1105	1110
Pro Ala Lys Arg Pro Arg Glu Thr Pro Ser Pro Ala Asp Pro Pro									1115									1120	1125
Gly Gly Ala Ser Lys Pro Arg Lys Leu Leu Val Ser Glu Leu Ala									1130									1135	1140
Glu Asp Pro Ala Tyr Ala Ile Ala His Gly Val Ala Leu Asn Thr									1145									1150	1155
Asp Tyr Tyr Phe Ser His Leu Leu Gly Ala Ala Cys Val Thr Phe									1160									1165	1170
Lys Ala Leu Phe Gly Asn Asn Ala Lys Ile Thr Glu Ser Leu Leu									1175									1180	1185

Lys Arg Phe Ile Pro Glu Val Trp His Pro Pro Asp Asp Val Ala
 1190 1195 1200
 Ala Arg Leu Arg Thr Ala Gly Phe Gly Ala Val Gly Ala Gly Ala
 1205 1210 1215
 Thr Ala Glu Glu Thr Arg Arg Met Leu His Arg Ala Phe Asp Thr
 1220 1225 1230
 Leu Ala
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 Ala Arg Ala Ala Ser Gly Phe Phe Ala Pro Ala Gly Pro Arg Gly Ala
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 Gly Arg Gly Pro Pro Pro Cys Leu Arg Gln Asn Phe Tyr Asn Pro Tyr
 35 40 45
 Leu Ala Pro Val Gly Thr Gln Gln Lys Pro Thr Gly Pro Thr Gln Arg
 50 55 60
 His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro Arg
 65 70 75 80
 Val Leu Asp Glu Asp Ala Pro Pro Glu Lys Arg Ala Gly Val His Asp
 85 90 95
 Gly His Leu Lys Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu Arg
 100 105 110
 Asp Val Leu Arg Val Gly Ser Gly Gly Phe Trp Pro Arg Arg Ser Arg
 115 120 125
 Leu Trp Gly Gly Val Asp His Ala Pro Ala Gly Phe Asn Pro Thr Val
 130 135 140
 Thr Val Phe His Val Tyr Asp Ile Leu Glu Asn Val Glu His Ala Tyr
 145 150 155 160
 Gly Met Arg Ala Ala Gln Phe His Ala Arg Phe Met Asp Ala Ile Thr
 165 170 175
 Pro Thr Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly His
 180 185 190
 Arg Val Ala Val His Val Tyr Gly Thr Arg Gln Tyr Phe Tyr Met Asn
 195 200 205
 Lys Glu Glu Val Asp Arg His Leu Gln Cys Arg Ala Pro Arg Asp Leu
 210 215 220

Cys Glu Arg Met Ala Ala Ala Leu Arg Glu Ser Pro Gly Ala Ser Phe
 225 230 235 240
 Arg Gly Ile Ser Ala Asp His Phe Glu Ala Glu Val Val Glu Arg Thr
 245 250 255
 Asp Val Tyr Tyr Tyr Glu Thr Arg Pro Ala Leu Phe Tyr Arg Val Tyr
 260 265 270
 Val Arg Ser Gly Arg Val Leu Ser Tyr Leu Cys Asp Asn Phe Cys Pro
 275 280 285
 Ala Ile Lys Lys Tyr Glu Gly Gly Val Asp Ala Thr Thr Arg Phe Ile
 290 295 300
 Leu Asp Asn Pro Gly Phe Val Thr Phe Gly Trp Tyr Arg Leu Lys Pro
 305 310 315 320
 Gly Arg Asn Asn Thr Leu Ala Gln Pro Arg Ala Pro Met Ala Phe Gly
 325 330 335
 Thr Ser Ser Asp Val Glu Phe Asn Cys Thr Ala Asp Asn Leu Ala Ile
 340 345 350
 Glu Gly Gly Met Ser Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe Asp
 355 360 365
 Ile Glu Cys Lys Ala Gly Gly Glu Asp Glu Leu Ala Phe Pro Val Ala
 370 375 380
 Gly His Pro Glu Asp Leu Val Ile Gln Ile Ser Cys Leu Leu Tyr Asp
 385 390 395 400
 Leu Ser Thr Thr Ala Leu Glu His Val Leu Leu Phe Ser Leu Gly Ser
 405 410 415
 Cys Asp Leu Pro Glu Ser His Leu Asn Glu Leu Ala Ala Arg Gly Leu
 420 425 430
 Pro Thr Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu Leu
 435 440 445
 Ala Phe Met Thr Leu Val Lys Gln Tyr Gly Pro Glu Phe Val Thr Gly
 450 455 460
 Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Leu Leu Ala Lys Leu Thr
 465 470 475 480
 Asp Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly Arg
 485 490 495
 Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys Arg
 500 505 510
 Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly Ile
 515 520 525
 Ile Thr Asp Lys Ile Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val Ala
 530 535 540
 Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp Ile
 545 550 555 560

Pro Ala Tyr Tyr Ala Ala Gly Pro Ala Gln Arg Gly Val Ile Gly Glu
 565 570 575
 Tyr Cys Ile Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys Phe
 580 585 590
 Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile Asn
 595 600 605
 Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr Cys
 610 615 620
 Leu Leu Arg Leu Ala Asp Gln Lys Gly Phe Ile Leu Pro Asp Thr Gln
 625 630 635 640
 Gly Arg Phe Arg Gly Gly Gly Gly Glu Ala Pro Lys Arg Pro Ala Ala
 645 650 655
 Ala Arg Glu Asp Glu Glu Arg Pro Glu Glu Glu Gly Glu Asp Glu Asp
 660 665 670
 Glu Arg Glu Glu Gly Gly Gly Glu Arg Glu Pro Glu Gly Ala Arg Glu
 675 680 685
 Thr Ala Gly Arg His Val Gly Tyr Gln Gly Ala Arg Val Leu Asp Pro
 690 695 700
 Thr Ser Gly Phe His Val Asn Pro Val Val Val Phe Asp Phe Ala Ser
 705 710 715 720
 Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu Cys Phe Ser Thr Leu
 725 730 735
 Ser Leu Arg Ala Asp Ala Val Ala His Leu Glu Ala Gly Lys Asp Tyr
 740 745 750
 Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe Phe Val Lys Ala His
 755 760 765
 Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg Asp Trp Leu Ala Met
 770 775 780
 Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser Ser Pro Glu Glu Ala
 785 790 795 800
 Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys Val Val Cys Asn Ser
 805 810 815
 Val Tyr Gly Phe Thr Gly Val Gln His Gly Leu Leu Pro Cys Leu His
 820 825 830
 Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu Met Leu Leu Ala Thr
 835 840 845
 Arg Glu Tyr Val His Ala Arg Trp Ala Ala Phe Glu Gln Leu Leu Ala
 850 855 860
 Asp Phe Pro Glu Ala Ala Asp Met Arg Ala Pro Gly Pro Tyr Ser Met
 865 870 875 880
 Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe Val Leu Cys Arg Gly

885					890					895					
Leu	Thr	Ala	Ala	Gly	Leu	Thr	Ala	Val	Gly	Asp	Lys	Met	Ala	Ser	His
			900					905					910		
Ile	Ser	Arg	Ala	Leu	Phe	Leu	Ser	Pro	Ile	Lys	Leu	Glu	Cys	Glu	Lys
			915					920					925		
Thr	Phe	Thr	Lys	Leu	Leu	Leu	Ile	Ala	Lys	Lys	Lys	Tyr	Ile	Gly	Val
			930					935					940		
Ile	Tyr	Gly	Gly	Lys	Met	Leu	Ile	Lys	Gly	Val	Asp	Leu	Val	Arg	Lys
					950					955					960
Asn	Asn	Cys	Ala	Phe	Ile	Asn	Arg	Thr	Ser	Arg	Ala	Leu	Val	Asp	Leu
				965					970					975	
Leu	Phe	Tyr	Asp	Asp	Thr	Val	Ser	Gly	Ala	Ala	Ala	Ala	Leu	Ala	Glu
			980					985					990		
Arg	Pro	Ala	Glu	Glu	Trp	Leu	Ala	Arg	Pro	Leu	Pro	Glu	Gly	Leu	Gln
			995				1000					1005			
Ala	Phe	Gly	Ala	Val	Leu	Val	Asp	Ala	His	Arg	Arg	Ile	Thr	Asp	
			1010			1015					1020				
Pro	Glu	Arg	Asp	Ile	Gln	Asp	Phe	Val	Leu	Thr	Ala	Glu	Leu	Ser	
			1025			1030					1035				
Arg	His	Pro	Arg	Ala	Tyr	Thr	Asn	Lys	Arg	Leu	Ala	His	Leu	Thr	
					1040	1045					1050				
Val	Tyr	Tyr	Lys	Leu	Met	Ala	Arg	Arg	Ala	Gln	Val	Pro	Ser	Ile	
			1055			1060					1065				
Lys	Asp	Arg	Ile	Pro	Tyr	Val	Ile	Val	Ala	Gln	Thr	Arg	Glu	Val	
			1070			1075					1080				
Glu	Glu	Thr	Val	Ala	Arg	Leu	Ala	Ala	Leu	Arg	Glu	Leu	Asp	Ala	
			1085			1090					1095				
Ala	Ala	Pro	Gly	Asp	Glu	Pro	Ala	Pro	Pro	Ala	Ala	Leu	Pro	Ser	
			1100			1105					1110				
Pro	Ala	Lys	Arg	Pro	Arg	Glu	Thr	Pro	Leu	His	Ala	Asp	Pro	Pro	
			1115			1120					1125				
Gly	Gly	Ala	Ser	Lys	Pro	Arg	Lys	Leu	Leu	Val	Ser	Glu	Leu	Ala	
			1130			1135					1140				
Glu	Asp	Pro	Ala	Tyr	Ala	Ile	Ala	His	Gly	Val	Ala	Leu	Asn	Thr	
			1145			1150					1155				
Asp	Tyr	Tyr	Phe	Ser	His	Leu	Leu	Gly	Ala	Ala	Cys	Val	Thr	Phe	
			1160			1165					1170				
Lys	Ala	Leu	Phe	Gly	Asn	Asn	Ala	Lys	Ile	Thr	Glu	Ser	Leu	Leu	
			1175			1180					1185				
Lys	Arg	Phe	Ile	Pro	Glu	Val	Trp	His	Pro	Pro	Asp	Asp	Val	Ala	
			1190			1195					1200				

Ala Arg Leu Arg Ala Ala Gly Phe Gly Ala Val Gly Ala Gly Ala
1205 1210 1215

Thr Ala Glu Glu Thr Arg Arg Met Leu His Arg Ala Phe Asp Thr
1220 1225 1230

Leu Ala
1235